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Occupational medicine and *Total Worker Health*®: from preventing health and safety risks in the workplace to promoting health for the total well-being of the worker

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Keywords: Health; safety; well-being; *Total Worker Health*; sustainability; decent work

Summary

The COVID-19 pandemic has highlighted the importance of Public Health interventions for global social and economic development. Still, the community's well-being depends on each individual's health. In addition to pandemics, health conditions can be altered by chronic degenerative diseases, aging, disabilities, and work. Personal behaviors such as poor nutrition, lack of physical activity, tobacco use, excessive alcohol consumption, and drug use can also affect health and safety at work. In the last twenty years, we have witnessed rapid changes in the nature of work, workplace and workforce. In parallel, there is increasing attention to fatigue, psychosocial risks and the achievement of decent, sustainable and healthy work as societal goals. Consequently, in 2011, NIOSH developed Total Worker Health®, a holistic approach to worker well-being to help improve worker health and safety. More recently, in Italy, the Ministry of Health has provided for the preparation of projects according to the "Total Worker Health (TWH)" approach in the National Prevention Plan for the five years 2020-2025. As indicated by the Ministry, the strategic role of the occupational physician is fundamental, being the only figure of occupational safety and health professionals able to integrate the health and safety of workers with their well-being to reach the Total Worker Health.

1. Introduction

The COVID-19 pandemic has affected everyone's life and impacted global social and economic development [1]. It has dramatically shown how the community's well-being depends on everyone's health. In addition to pandemics, health can be altered not only by chronic degenerative diseases, aging, and disability but also by personal behaviors such as poor nutrition, lack of physical activity, tobacco use, excessive consumption of alcohol and use of other drugs [2-4].

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In this regard, in the constitution of the World Health Organization (WHO), adopted by the International Health Conference held in New York in 1946, health was defined as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [5]. Forty years later, at the 1st International Conference on Health Promotion held in Ottawa in 1986, the WHO reported in the Ottawa Charter for Health Promotion that "To reach a state of complete physical, mental and social well-being, an individual or group must be able to identify and to realize aspirations, to satisfy needs, and to change or cope with the environment. Health is, therefore, seen as a resource for everyday life, not the objective of living." [6]. As a result, it is pretty intuitive that people should be able to fulfil their aspirations and meet their needs in every field of their existence, including communities, home, and working life, to be considered healthy. In addition with regard to work, if we keep in mind that usually, a work shift lasts about 8 hours, it follows that people spend a third of their working day in the workplace. According to what is defined by the WHO, it is unthinkable that workers can be considered healthy if they are not able to fulfil themselves and adequately deal with the work environment. Indeed, their prerogatives define the possibility of achieving a state of complete physical, mental and social well-being [5].

In the last twenty years, we have witnessed rapid changes in the nature of work, workplace and workforce. In parallel, there is increasing attention to fatigue, psychosocial risks and the achievement of decent, sustainable and healthy work as societal goals [7]. According to the WHO, a workplace should possess several characteristics to be healthy, safe and resilient [8]. First, it should be an environment where workers can perform their tasks without falling victim to illness or injury due to their work. However, at the same time, the workplace should be able to provide them with the opportunity to improve their physical and mental health and, more generally, their overall well-being.

Moreover, a healthy, safe and resilient workplace should allow the worker to be in harmony with the surrounding nature and be protected when a catastrophic event occurs. In this context, the WHO [8] has also defined strategies and initiatives that aim to increasingly improve health and safety conditions in the workplace to achieve healthier, safer and more resilient workplaces for all. These interventions include: (i) the support to the development and subsequent practical implementation of national policies and action plans that are focused on protecting both workers' health and safety and the environment; (ii) the development of evidence-based programs for the prevention of occupational risks (physical, chemical, biological and psychosocial); (iii) the control and monitoring of both occupational and work-related diseases and accidents at work; (iv) the promotion of all workers' health, safety and well-being, including migrants and those in precarious working conditions; and (v) the establishment of workplace resilience against extreme climatic events, atmospheric pollution, industrial disasters and pandemics.

It is, therefore, inevitable that the achievement of a safe, healthy, and resilient workplace can only be achieved by a holistic approach that, on the one hand, protects the health and safety of workers through the prevention and protection from risks at work, from other through their health promotion. Critical to health promotion is not telling workers what to do but removing obstacles so they can make healthful choices.

In this perspective, we aim to describe the Total Worker Health (TWH) approach that has this purpose and its governmental applications in Italy and to provide some reflections on the importance of the occupational physician (OP) for its application in work settings.

2. Total worker health

The origin of TWH (Figure 1) dated to 2003 when National Institute for Occupational Safety and Health (NIOSH) developed the "NIOSH Steps to a Healthier US Workforce Initiative", which aimed, in addition to healthy and safe work, to have environments that support health and access to adequate health care for protecting, supporting and improving the health of workers. In 2005, NIOSH developed the WorkLife initiative, addressing the health and well-being of workers more comprehensively and considering the physical and

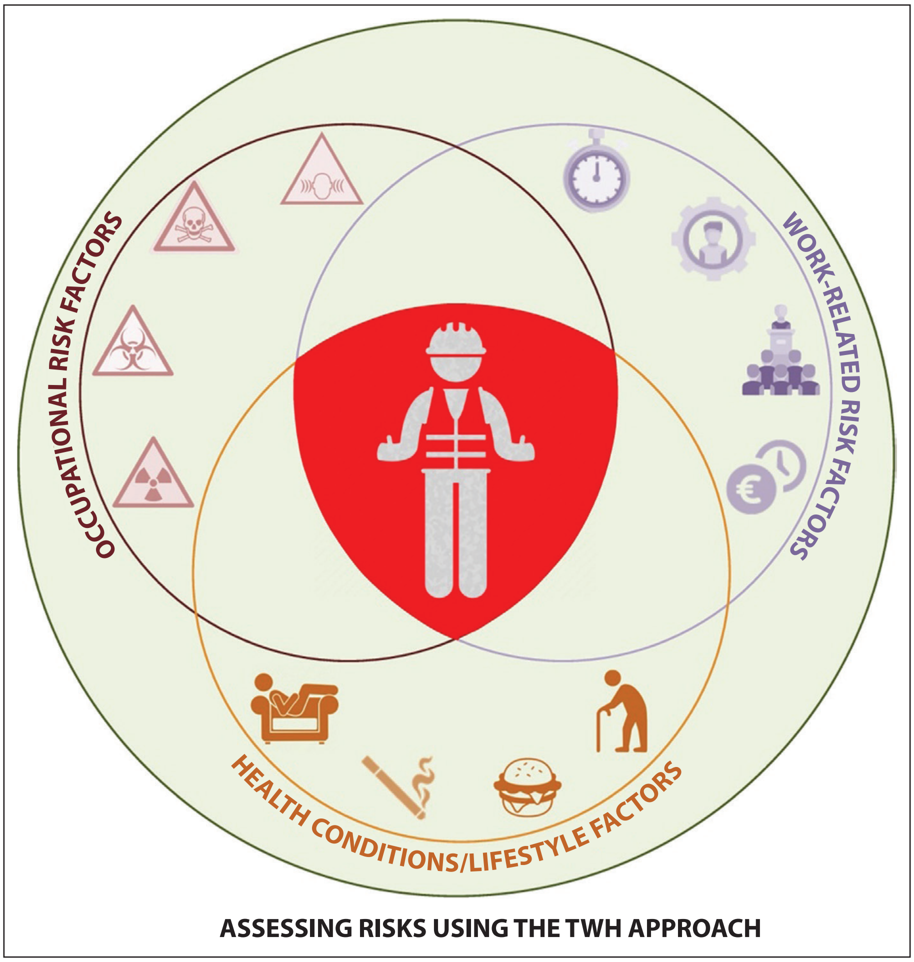

Figure 1. The integrated TWH approach to assessing risks that threaten worker health and well-bing. This model focuses on how the OSH system can better understand the adverse health effects correlated to the workers' exposure to occupational and/or job-related risk factors, while taking into account the individual health conditions/lifestyle risk factors that may be present. Assessing and mitigating all of these risks is an essential step to improve the overall safety, health and well-being of workers.

organizational work environment and individual behaviors. In 2011, the WorkLife was renamed the *Total Worker Health* Program, defined "as policies, programs, and practices that integrate protection from work-related safety and health hazards with promotion of injury and illness-prevention efforts to advance worker well-being" [9].

More recently, NIOSH published a workbook "Fundamentals of *Total Worker Health*® Approaches" (2016), focusing on five defining elements that are: "(i) demonstrate leadership commitment to worker safety and health at all levels of the organization; (ii) design work to eliminate or reduce safety and health hazards and promote worker well-being; (iii) promote and support worker engagement throughout program design and implementation; (iv) ensure confidentiality and privacy of workers; (v) integrate relevant systems to advance worker well-being" [9].

3. Total worker health in Italy

In Italy, the concept of health promotion, as well as the design, implementation and practical application of interventions aimed at improving the health conditions of workers in the workplace, is an integral part of the regulatory framework governing the protection of health and safety in the workplace. Indeed, article 25 of Legislative Decree 81/08, which sets out the obligations of the OP, states that the tasks of this professional figure also include collaboration in the implementation and enhancement of voluntary health promotion programs, according to the principles of social responsibility [10]. In this regard, it should be noted that, according to the decree mentioned above, one of the main tasks of OPs, by conducting the health surveillance medical examinations, is to assess and issue the fitness for work, that is to evaluate, considering exposure to various occupational risk factors, the suitability of workers for specific tasks, thus guaranteeing a satisfactory fit between person and job [11]. However, to enable workers to perform the work for which they have been hired in a safe and healthy manner, it is also necessary for the OP to take due account of any diseases, health issues or disabilities that might hinder the proper and secure performance of working tasks [12]. Therefore, based on these considerations, it is not surprising that the reference Italian regulatory framework on health and safety protection in the workplace also gives the OPs a leading role in implementing health promotion programs.

The medical nature of this professional figure, combined with an understanding of the many critical aspects of occupational exposures and the in-depth knowledge of workers' health conditions, allows the OP to hold a privileged position to contextualize the theoretical principles of health promotion in individual production sites. The OP can therefore implement effective programs tailored to workers' needs, thus fully realizing the role of collaboration and support to the employer as established by law. Despite the many issues associated with technological progress, climate change, work organization, the ageing workforce and, last but not least, the pandemic, Occupational Medicine (OM), is continuously evolving to respond to these stresses. Born as a clinical discipline, OM is mainly concerned with prevention [13]. In this context, OM, and in particular OPs who are integral parts of the occupational safety and health (OSH) system, represent the natural interlocutor and recipient of TWH strategies, methodologies and policies. Indeed, applying the TWH principles would not lead to a distortion of the OM essence but rather to an extension of its primary preventive scope. A global assessment of all the risk factors calls for integrating occupational, work-related, and individual traits influencing workers' health and well-being.

Indeed, the strategic role of the OPs for the TWH model is further recalled and strongly emphasized by the Italian Ministry of Health through National Prevention Plan (NPP) for the five years 2020-2025 [14]. Here, the TWH approach is referred to in the Central Support Line no. 3, "Activation of technical tables for the strengthening of the overall health of the worker according to the *Total Worker Health* approach". Line no. 3 aims to activate processes and interventions to make the workplace a health-friendly environment. In agreement with the TWH principles, the NPP pointed out that this objective must be pursued through the involvement of all prevention professionals, including the OP. Similarly, the TWH is also mentioned within the macro-objective M04, "Injuries and accidents at work, occupational diseases". TWH is an effective intervention methodology addressing the various factors with a potentially negative impact on the work organization and the workforce's health. In planning the prevention policies and interventions, TWH would allow for adequately considering the synergy between work-related risks, environment, lifestyles and personal health conditions.

The main OM objective would be to implement a worker protection model evolving from the prevention of accidents at work and occupational diseases towards the "active preservation" of workers' health through a multidisciplinary approach involving the strengthening of the collaboration network between OPs, other health professionals, territorial and hospital services and general practitioners (GPs). The NPP highlighted that a primary line of action to achieve the aim mentioned above is the promotion of the strategic role of OPs in the design, implementation and monitoring of TWH and health promotion interventions (Figure 2). In addition, the TWH approach is also mentioned in several predefined programs (PP), such as in PP3 "Workplaces that promote health", PP4 "Addictions", PP6 "Targeted prevention plan", PP7 "Prevention in

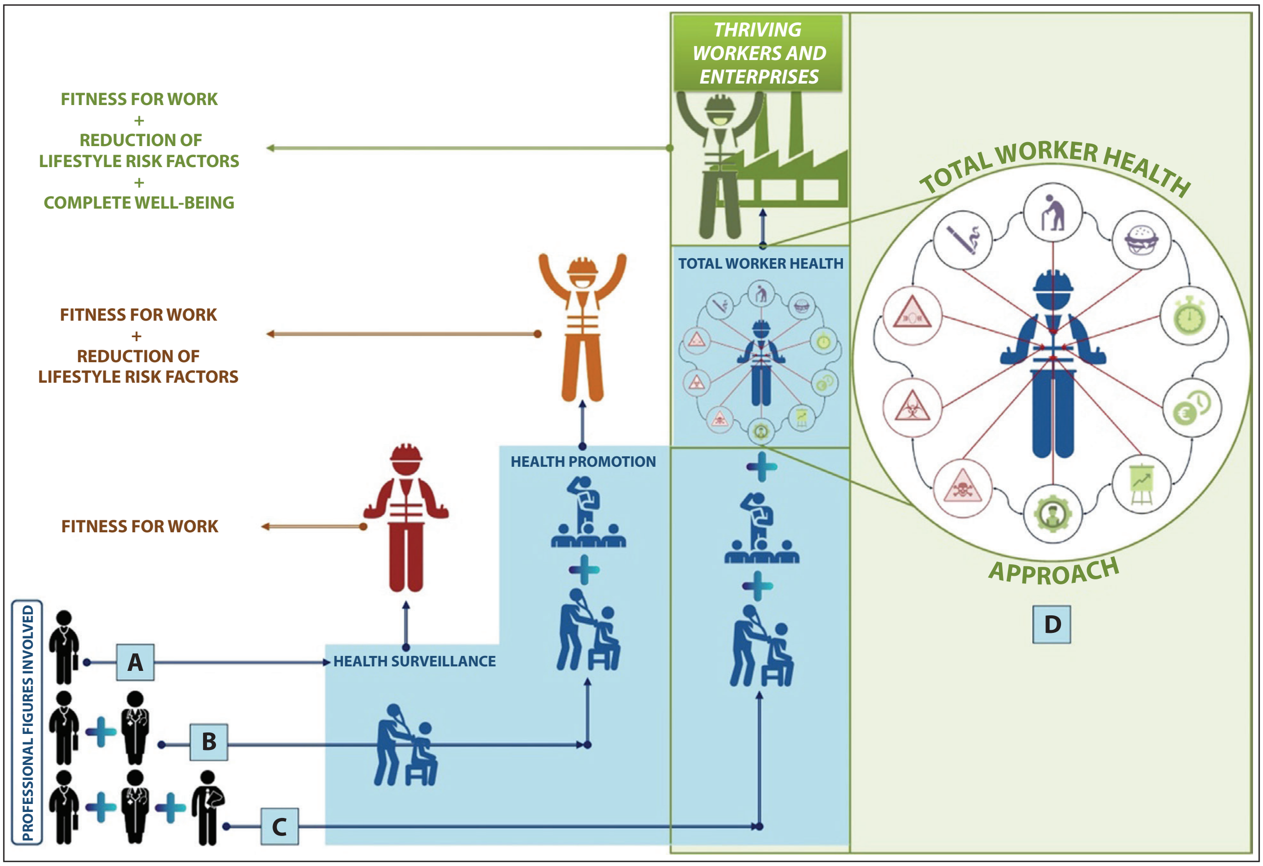

Figure 2. The added value of the TWH approach to the OSH system activities. **A:** Traditionally, OSH protection programs are focused on guaranteeing that work is safe and that workers are protected from occupational risk factors. In this context, the OPs carry out the health surveillance medical examination in order to verify and assess their suitability for specific working tasks; **B:** A good collaboration between the OPs and the other physicians should be able to guarantee workers greater protection of their health. One of the main areas in which this interaction can materialise is in the field of health promotion, which is not only indicated by the the American College of Occupational and Environmental Medicine as one of the most important occupational physician additional knowledge and skill [15], but is also an integral part of the Italian regulatory framework governing the protection of health and safety in the workplace; **C:** The aim of the TWH approach is to achieve a working environment that is as free as possible of risks and hazards that may compromise the safety and health of workers, but at the same time its policies, programs, and practices aim to promote the complete well-being of workers; **D:** In this regard, the TWH model implements a robust culture of safety, worker protection, and greater health opportunity through the analysis of both occupational and/or work-related risk factors and personal health conditions and/or lifestyle factors and the evaluation of the possible interactions and reciprocal influences between all these elements.

construction and agriculture", and PP8 "Prevention of professional cancerogenic risk, of occupational diseases of the musculoskeletal system, of work-related stress risk". For this reason, on 15 June 2022, the Italian Society of Occupational Medicine (SIML) approved the establishment of a working group on health promotion to identify the knowledge and needs of OPs on this issue to support them in developing health promotion initiatives in the workplace which also consider the TWH approach.

Building up a bridge between hospitals and the territory is a significant challenge for health managers, but building a bridge between OPs and GPs is an OM's critical objective. OM is concerned with an important part of the population and should represent a crucial node in the network being built up to implement proximity medicine [16]. Integrating both joint and complementary activities (e.g., GP's and OP's common education efforts to implement prevention programs, GP's proximity care, OP's return to work after acute illness or exacerbation of chronic diseases) is a challenging task that should be addressed within an innovative and modern alliance to be built up among OSH professionals and proximity care network based on GPs. Converging efforts of all physicians concerned with workers' health is necessary to ensure the long-term sustainability of the Italian universalistic health system.

4. Conclusions

The OP is fundamental and strategic for implementing TWH interventions. OP, collaborating with other OSH professionals, can allow the integration between the prevention and protection measures against risks at work and the promotion of the health and well-being of workers according to a *Total Worker Health* approach. It is known that the current hierarchy of control is a system for controlling risks in the workplace based on a risk assessment and management without due consideration to inter-individual differences among workers. It is carried out on workers' homogeneous groups exposed to the same risks, irrespectively of the individual health and well-being that only the OP, treating sensitive health data, can know. It follows that through TWH interventions, it is possible to reach a targeted risk assessment and management that allows for workforce and personalized prevention. The effective integration of OP's workplace health promotion with proximity care may depend on many factors such as the characteristics of national health systems and the relative existing contributions of the public and private sectors. In this regard, OPs and other physicians involved in the care of the worker/patient should integrate their roles and activities with the fundamental principles of the TWH in such a way as to guarantee subject with health and preventive services that protect them comprehensively, enabling them to achieve an overall and satisfactory state of well-being.

Declaration of interest: The authors declare no conflict of interest. The findings and conclusions of this report are those of the authors do not represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and prevention or other affiliate organizations of the authors. P.A. Schulte served as a contractor to NIOSH.

References

1. OECD (2021), COVID-19 and Well-being: Life in the Pandemic, OECD Publishing, Paris, https://doi.org/10.1787/1e1ecb53-en
2. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019 [published correction appears in *Lancet*. 2020 Nov 14;396(10262):1562]. *Lancet*. 2020;396(10258):1204-1222. Doi:10.1016/S0140-6736(20)30925-9.
3. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases Writing Group. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol*. 2020 Dec 22;76(25):2982-3021.
4. GBD 2016 Alcohol and Drug Use Collaborators. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Psychiat*. 2018 Dec;5(12):987-1012.
5. World Health Organization (WHO). Constitution of World health Organization. International Health Conference, New York, 1946. Available on line at: https://apps.who.int/gb/bd/PDF/bd47/EN/constitution-en.pdf?ua=1 (Accessed on 15 September 2022).
6. World Health Organization (WHO). The Ottawa Charter for Health Promotion. 1st International Conference on Health Promotion. Ottawa, 1986. Available online at: https://www.who.int/teams/health-promotion/enhanced-wellbeing/first-global-conference#:~:text=To%20reach%20a%20state%20of,not%20the%20objective%20of%20living. (Accessed on 15 September 2022).
7. Schulte PA, Iavicoli I, Fontana L, et al. Workgroups on the Future of Decent Work and Demographic Changes and Occupational Health. Occupational Safety and Health Staging Framework for Decent Work. *Int J Environ Res Public Health*. 2022; 19(17):10842. Doi: 10.3390/ijerph191710842.
8. WHO (2022) Promoting healthy, safe and resilient workplaces for all Available online at: https://www.who.int/activities/promoting-healthy-safe-and-resilient-workplaces-for-all
9. Lee MP, Hudson H, Richards R, et al. on behalf of the NIOSH Office for Total Worker Health,

Fundamentals of total worker health approaches: essential elements for advancing worker safety, health, and well-being. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 2017-112, December 2016.
10. Decree Law 9 April 2008 no. 81. Implementation of Article 1 of the Law 3 august 2007 no. 123, concerning the protection of health and safety in the workplace.
11. Persechino B, Fontana L, Buresti G, et al. Collaboration of occupational physicians with national health system and general practitioners in Italy. *Ind Health*. 2017;55(2):180-191. Doi:10.2486/indhealth.2016-0101
12. Persechino B, Fontana L, Buresti G, Fortuna G, Valenti A, Iavicoli S. Improving the job-retention strategies in multiple sclerosis workers: the role of occupational physicians. *Ind Health*. 2019;57(1):52-69. Doi:10.2486/indhealth.2017-0214
13. Persechino B, Fontana L, Buresti G, et al. Professional activity, information demands, training and updating needs of occupational medicine physicians in Italy: National survey. *Int J Occup Med Environ Health*. 2016;29(5):837-858. Doi:10.13075/ijomeh.1896.00736
14. Ministero della Salute. Direzione Generale della Prevenzione Sanitaria. Piano Nazionale della Prevenzione 2020-2025. Available online at: https://www.salute.gov.it/imgs/C_17_notizie_5029_0_file.pdf (Accessed on 15 September 2022).
15. Cloeren M, Gean C, Kesler D, et al. American College of Occupational and Environmental Medicine's Occupational and Environmental Medicine Competencies-2014: ACOEM OEM Competencies Task Force*. *J Occup Environ Med*. 2014;56(5):e21-40. Doi: 10.1097/JOM.0000000000000173
16. Beaulieu MD. The perils and the promise of proximity: Dr Ian McWhinney Lecture, 2016. Can Fam Physician. 2016 Dec;62(12):964-968.

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The role of chance in cancer causation

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Keywords: Cancer causation; susceptibility; carcinogenesis; cancer prevention

Summary

In the last years, the discussion about the role of chance in the causation of cancer has generated a large scientific and public debate. The concept that chance, or "bad luck", as responsible for a majority of the variation of cancer incidence, may be misleading, possibly causing an underestimation of the role played by known risk factors. In this commentary we discuss how host and external factors interact with chance in cancer causation in different ways, and provide examples of situations where chance appears to play only a minor role on cancer onset.

1. Introduction

As causal factor for cancer, chance has been described as "bad luck", "intrinsic replicative factor", "unpreventability", "intrinsic random factor" [1, 2] and, specifically for cancers, a "stochastic event" [3].

According to Tomasetti and Vogelstein [4, 5], two thirds of the variation in cancer rates across different tissues and organs could be explained by random mutations occurring during DNA replication, a concept they referred to as "bad luck". However, such hypothesis sparked criticism [6] in the scientific community due to a number of reasons, including: (i) the authors' assumptions, such as the use of mouse data to derive human stem cell division rates [7]; (ii) the emphasis on rare cancers, coupled with the exclusion of common cancer types due the lack of data; and (iii) the possible detrimental effects on public health perspective driven by the article if misinterpreted, suggesting the need for a greater focus on secondary prevention of cancer rather than primary prevention [8]. Besides, in contrast with the "bad luck" hypothesis, subsequent reports confirmed previous evidence that environmental factors play a key role in explaining cancer risk and that the rates of mutation occurring by chance alone cannot explain cancer risk without taking into consideration extrinsic factors [9, 10].

A necessary condition for cancer development is a sequence of genetic mutations [11, 12] escaping DNA-repair systems.

Although chance is considered to play a prominent role in some cases [4], additional factors appear to be crucial in cancer causation, such as the immune system, hereditary factors and the DNA damage response. In addition, the environmental exposure is also known to be involved in cancer occurrence [13, 14]. In this commentary, we discuss how host and external factors interact with chance in cancer causation in different ways. Also, we provide examples of situations where chance plays only a minor role on cancer onset.

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1.1 Environmental factors

Literature accounts many carcinogen agents, which have been deeply studied in relationship to different cancer types and which have been classified by IARC [15]. Known carcinogens include high prevalence factors, such as arsenic, asbestos and tobacco smoking, to low prevalence ones, including infectious agents which are endemic in restricted areas (e.g. Clonorchis sinensis) or chemicals (e.g. aromatic amines) which currently are rarely used, or continue to be used in small subgroups of the population worldwide. Exposure to environmental carcinogens typically leads to cancer in a minor proportion of the exposed subjects. For a given carcinogen, the magnitude of the risk of cancer depends on different exposure-related factors, including dose (cumulative exposure), dose-rate (quantity of exposure within a certain time interval), intensity and duration of exposure, the co-presence of other agents (e.g. mineral dust for radon decay products, where the exposure to α-particles is conditional to mineral dust inhalation [16]) which may reciprocally interact, as well as host-related factors including genetic susceptibility, family history of cancer [17] and chance [3].

Even after prolonged exposure to ascertained carcinogens, the cumulative risk of cancer in the exposed rarely exceeds 25% compared to the unexposed. For example, the absolute risk of lung cancer in heavy, long-term smokers is in the order of 20-30% [18]. However, few examples of circumstances of exposure to environmental carcinogens in which all – or an overwhelming proportion of – the exposed subjects were diagnosed with cancer can be identified. A well-known example is that of occupational exposure to aromatic amines in the dye production industry. Following anecdotal reports and experimental studies in dogs [19], the carcinogenicity of aromatic amines such as 2-naphthylamine and benzidine was demonstrated in the 1950s in a cohort of British chemical workers [20]. The study included 4,622 men employed in 21 plants in which workers were exposed to aniline, benzidine, 2-naphthylamine or 3-naphthylamine. A large excess of bladder cancer was noticed in this cohort, in particular among those exposed to aniline and 2-naphthylamine.

Other studies subsequently reported an increased risk of bladder cancer in workers exposed to 2-naphthylamine, benzidine, and 4-aminobiphenyl [21], with heterogeneity in the risk estimates, likely reflecting different levels of exposure and other possible circumstances. In one of the plants included in the first study, however, all 15 workers involved in the distillation of 2-naphthylamine developed bladder cancer [22]. This result shows that, in exceptional situations of exposure to environmental carcinogens, chance no longer operates, except possibly in determining the timing of cancer onset.

1.2. Hereditary factors

Genetic syndromes with high penetrance are a remarkable example of the different role that chance might play in cancer causation at individual level.

Indeed, a situation in which all the individuals with a specific mutation develop the related disease or phenotype, can be considered an example of exclusion of chance from the etiologic pathway. For instance, as reported by previous studies in mice [23], *Rb1* is the most frequently mutated gene in the pediatric retinoblastoma (Rb), and its loss causes E2F transcription factors to induce proliferation-related genes. Co-deletion of *Pten* with *Rb1* and *Rbl1* in mouse retinal progenitor cells causes fully penetrant bilateral retinoblastomas by 30 days and strongly suppresses Rb/E2F-induced apoptosis [23], while germline mutations in humans lead to 90-95% penetrance [24] and 95% of Rb patients are diagnosed by the age of 5 [25].

Another good example is Multiple endocrine neoplasia type 1 (MEN1), an autosomal dominant disorder characterized by parathyroid, pancreatic islet, and anterior pituitary tumors. The MEN1 gene, a tumor suppressor gene, had been localized to chromosome 11q13. Different studies [26, 27] demonstrated that the penetrance of this disease rises steadily with age, from 7% in the <10-years-old to 100%, by the age of 60.

In these examples of genetic syndromes with high penetrance, the hereditary factor seems to be the only sufficient causal factor for developing a tumor at some point in life, practically excluding the role of chance that would, otherwise, interfere in a proportion of the cases.

However, syndromes caused by genetic variants with incomplete penetrance may also provide valuable examples for the role of factors other than genetics, including chance, in the occurrence of diseases at the individual level. For instance, germline mutations in the Rearranged during Transfection (RET) proto-oncogene are associated with the Multiple endocrine neoplasia type 2 (MEN2) hereditary syndrome, though not all the individuals carrying such mutations develop all cancers and non-neoplastic diseases commonly associated with the syndrome, the most common being medullary thyroid carcinoma and pheochromocytoma [28]. Such phenotypic differences are linked to different mutations in the RET gene, albeit these do not entirely explain interindividual variability [29]. While a need for further genetic events (second-hit) in the RET gene has also been suggested for cancer development, the role of other factors, such as environmental factors, stochastic events involving also epigenetic modifications, may be significant. In addition, the factors leading to this second hit are not known [30], and the role of chance cannot be excluded in this context as well. Similarly, factors determining epigenetic differences which may lead to different phenotypes are not well understood [30-32] and, while one could argue that we still do not have a complete understanding of the individual contributions of genetics and environmental factors, the potential effect of stochastic events cannot be ruled out.

Unlike all the syndromes mentioned above, which are associated with specific types of tumors, Li-Fraumeni syndrome is characterized by the great variability of organs and type of neoplasms involved. This hereditary condition connoted by alterations on p53, one of the main tumor suppressor proteins, is due to genetic mutation on the TP53 allele on chromosome 17.

A large cohort study investigated cancer epidemiological and phenotypical aspects in subjects with p53 mutations. Li-Fraumeni syndrome carries a nearly 100% risk of cancer by age 70, causing leukemia, lymphoma, gastrointestinal, head and neck, kidney, larynx, lung, skin melanoma, ovary, pancreas, prostate, testis and thyroid cancers [33, 34].

An opposite example is Laron syndrome (LS). This disease, also called primary growth hormone resistance, is characterized by congenital deficiency of insulin-like growth factor 1 (IGF1).

A cohort study of 230 LS patients [35], 116 isolated growth hormone (IGH) deficiency patients, 79 patients with Growth-hormone-releasing hormone (GHRH) defects and 113 congenital multiple pituitary hormone deficiency (MPHD) patients reported a surprising low number of cancer cases. In particular, none of the 230 LS patients developed cancer at the time of the study. Knock-out mouse models supported these observations in humans [35]. It appears, therefore, that lack of IGF1 is associated with a null or very low risk of cancer, despite the presence of other environmental, lifestyle, socioeconomic and epigenetic factors.

We must add that studies on LS and cancer incidence [35] are usually characterized by small populations of relatively young patients.

1.3. DNA damage response

As mentioned above, Tomasetti and Volgestein [4] suggested that the lifetime risk of cancer in different tissues is strongly correlated with the total number of divisions of their stem cells, due to driver gene mutations that randomly result from the DNA duplications.

If we took this model literally, we could say that, if cancer does indeed mainly depend on the total number of divisions of stem cells, then taller, bigger individuals, whose cells would have gone through more divisions during the phases of development and generally throughout life, should have higher incidences of cancer. This does indeed appear to be true, with taller, bigger individuals having been proved my multiple studies to have a higher risk of developing various types of cancer when compared to smaller individuals [36], both in the case of humans and in that of animals, for example when considering the different cancer rates between different dog breeds [37].

However, if this applies quite well when considering different individuals within a species, the situation appears different when moving from an animal species to another one: we would expect that bigger animal species, having more cells than smaller ones, and therefore having undergone more cell divisions throughout their lives in order to reach that number of cells, would also show significantly higher incidences of cancer. However, this is far from being the case, and it seems that, on the contrary, large species of animals show low incidences of cancer, as is the case for whales or elephants [38]. This phenomenon is known as Peto's paradox, and seems to suggest that the role of the total number of stem cell divisions might be essential for the development of cancer in certain single species, but might not be valid across the entire animal kingdom [39].

If we consider elephants, they show a cancer mortality rate of 4,8% [40], lower if compared to the human one (11-39%) [41], despite the fact that elephants can weight up to 100 times more than humans. According to recent studies [40, 42], this seems to be at least partially due to the fact that elephants possess an enhanced DNA damage response mechanism, comprising 20 copies of TP53 encoded throughout their genome. This led to the fact that elephant cells undergo p53-mediated apoptosis at a higher rate in response to DNA damage, when compared to human cells [42]. This seems to show that, even in the case of higher DNA damage, and despite a significantly higher level of lifetime cell divisions, elephant cells are better suited at responding to DNA damage than human ones.

Finally, we could say that, although the gross stochastic effect of DNA replication, and thus chance, could indeed be considered an important contributor to cancer development, one should also take into account the role of processes such as DNA damage repair and antitumoral immunity, which do not depend on chance but, on the contrary, are finalized at reducing the unorderly effects caused by chance.

In fact, out of thousands episodes of DNA damage per stem cell per day, few remain unaddressed by the cellular DNA damage response mechanisms, and are thus potentially lead to mutation in the daughter cells. Even fewer of those mutations will produce neoplastic cells, while most will be neutralized (or, at least kept at bay) by the organism's antitumor immune response [43].

It can be therefore concluded that chance may manifest insofar the organism leaves it the space to do so: in species, individuals or single tissues where DNA damage repair and antitumoral immunity are impaired, the role of chance could be enhanced and the effect of overall divisions on mutations and cancer would be paramount. On the other hand, in cases where the tumoral development can be hindered by DNA damage repair or antitumoral immunity, the role of chance is reduced, and so is the incidence of cancer caused by spontaneous cell divisions.

1.4. The immune system

Another important component playing a crucial role in the development of cancer, is antitumoral immunity. Its important role is clearly shown in small bowel cancer (SBC), which represents an outlier in terms of incidence of neoplasms in humans. In fact, despite the high-replication rhythm of the intestine's epithelium and the large dimension of the organ, the small bowel is rarely affected by cancer, in particular by adenocarcinoma [44], the most common type of cancer in neighboring digestive organs. SBC collectively account for only 2% of cancers of the digestive system.

The SB surface is approximately 15 times larger [45] than that of colon-rectum and even though SBC and colorectal cancer (CRC) share several risk factors [46, 47], the age-standardized rate of SBC in the US is around 20 times lower than that of CRC [48]. Based on these figures, one can estimate that the incidence of SBC is roughly 300 times lower than that of CRC per surface unit.

This epidemiological peculiarity appears to be in contrast with the model proposed by Tomasetti and Vogelstein [4]. In fact, these authors assumed that endogenous mutation rates are nearly identical across all cell types, and therefore the lifetime risk of developing cancer in a particular organ or tissue should correlate with the lifetime number of stem cell divisions in that organ or tissue [4]. According to this model, a tissue whose stem cells undergo a high overall number of divisions would therefore be more likely to develop multiple somatic driver mutations, which in turn would kick off the process of oncogenesis and eventually lead to cancer [4].

One explanation for this phenomenon is the fact that different tissues, and even different cell types within the same tissue, respond differently to DNA damage [49]. For example, SB stem cells appear to be extremely sensitive to DNA damage and, in experimental settings, undergo massive apoptosis upon low doses of irradiation (1 Gy) [50]; on the contrary, colonic stem cells require eight-time higher level of irradiation in order to undergo apoptosis; they also display a lower expression of p53 and a higher expression of bcl2 compared to SB stem cells [50].

Furthermore, other protective mechanisms and peculiarity of small intestine's mucosa have been hypothesized to exert an anti-cancer effect, including a rapid cell turnover, the relatively small bacterial load, an alkaline environment, the rapid content transit, the low level of activating enzymes of pre-carcinogens and the greater mucosal lymphoid infiltration than in the CR [47, 51, 52]. Moreover, the rapid transit of SB content and the reduced contact time of bowel's mucosa with carcinogens were hypothesized to diminish the risk of cancer compared to CR [51]. In conclusion, the characteristics of the anti-tumoral immunity in these tissues may explain, at least partially, the difference in cancer occurrence between SB and CR. While the immune system's impairment (either dependent from a disease or iatrogenic) increases the risk of cancer occurrence, especially in case of infection-associated neoplasms, the role of chance and its interaction with the anti-tumoral response cannot be excluded.

1.5. Chance, including gene-environment interaction

In the present commentary, we presented examples of conditions in which chance seems to play a minor role in the development of a tumor. Knowing that cancer is a multifactorial disease, and given the presence of chance, it is very difficult to assess which are the necessary causal factors for a specific type of cancer and for a specific patient.

Cancer epidemiology has the valuable ambition to identify and characterize the risk factors of the different types of cancer. To do this, different measures of estimate are used, such as population attributable fraction (PAF). Anyway, such measures apply to the general population – or in more or less large groups of population – rather than on the single individual [53].

A major obstacle in assessing the role of each carcinogenic factor derives from the imprecision of the measures we use to attribute a cancer to a specific event.

If we were able to predict with extreme precision which individual, who has the necessary combination of causal factors, will develop a certain type of cancer, we cannot tell in which moment it's going to happen or if the patient's life is going to be threatened by further diseases. The function of chance in determining the time of onset of a disease is poorly understood. Many other host factors could interact with chance in determining the timing of onset of cancer, including hereditary factors, epigenetics, the immune system and the anti-tumoral response.

Indeed, the increase of probability of an outcome and its anticipation in time are two aspects of the same phenomenon. Our capacity to observe the occurrence of an event is, in fact, determined by the period of observation and by the lifespan of the individual, and it is not possible to know whether a cancer occurring at time t_0 in an exposed individual would have occurred, in the absence of exposure, at time $t_0 + t_1$ or would not have occurred at all. Accelerated failure time models are used to reduce these limitations in the estimation of cancer incidence, survival and onset [54].

Possible examples of chance as "timer" of the onset of a cancer could be some of the high penetrance genetic syndromes cited above, specifically MEN1 and Li Fraumeni syndrome. Patients affected by these conditions have practically 100% probability to develop a tumor, even if with great variability for the age of onset [26, 27, 33, 34]. On the contrary, almost all Rb patients (95%) are diagnosed before 5 years of age; this difference could imply a lesser role of chance or a stronger oncogenic power of the associated genetic mutation of this syndrome.

2. Conclusions

Based on Tomasetti and Volgestein model [4], the effect of chance on cancer causation is expected to increase with age, due to the lifetime number of stem cell divisions and consequently, the accumulation of somatic mutations. Accordingly, there is an increasing trend between age and cancer rate, reaching its peak at 75 to 85 years of age, after which a decrease takes place [55-60]. Even though some possible explanations have been described [58], this phenomenon is still to be completely understood.

However, modern medicine is more and more interested in understanding the causes of cancer, especially when aiming at primary and secondary prevention. In fact, as our knowledge about the other variables grows, the contribution of chance in the causation of cancer reduces. Unlike chance, many carcinogenic factors have been described and are increasingly easier to detect and to remove. In the last years, secondary prevention has been implemented in many countries for breast [61], colorectal [62] and cervical [63] cancer and a significant progress is being made for prevention of liver cancer due to Hepatitis C Virus infection [64, 65], of lung cancer in heavy smokers [66-68] and of Helicobacter pylori-associated gastric cancer [69-71]. Furthermore, several successful interventions in cancer control have been made, such as the introduction of Hepatitis B and Human Papillomavirus vaccinations and of limits of occupational exposure to carcinogens.

From this point of view, public health and occupational medicine play major roles in cancer prevention with benefits in terms of global burden of disease.

Finally, if we were able to prevent any cancer, extending the overall life expectancy, the incidence of many other diseases would probably increase, just because people would live longer enough to develop these other conditions, that are, as cancer, associated with aging. This also applies in reverse; cancer would be more relevant as progress is made in treating or preventing any other disease, leaving cancer the main health focus.

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References

1. Perduca V, Alexandrov LB, Kelly-Irving M, et al. Stem cell replication, somatic mutations and role of randomness in the development of cancer. *Eur J Epidemiol.* 2019;34(5):439-445.
2. Weinberg CR, Zaykin D. Is bad luck the main cause of cancer?. *J Natl Cancer Inst.* 2015;107(7):djv125. Published 2015 May 8.
3. Luzzatto L, Pandolfi PP. Causality and Chance in the Development of Cancer. *N Engl J Med.* 2015;373(1): 84-88.
4. Tomasetti C, Vogelstein B. Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science*. 2015;347(6217):78-81.
5. Tomasetti C, Li L, Vogelstein B. Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science*. 2017;355(6331):1330-1334.
6. Couzin-Frankel J. Science Communication. Backlash greets “bad luck” cancer study and coverage. *Science*. 2015;347(6219):224.Doi:10.1126/science.347.6219.224
7. Rozhok AI, Wahl GM, DeGregori J. A Critical Examination of the “Bad Luck” Explanation of Cancer Risk. *Cancer Prev Res* (Phila). 2015;8(9):762-764.
8. Most types of cancer not due to “bad luck” IARC responds to scientific article claiming that environmental and lifestyle factors account for less than one third of cancers. *Cent Eur J Public Health*. 2015; 23(1):87.
9. Wu S, Powers S, Zhu W, Hannun YA. Substantial contribution of extrinsic risk factors to cancer development. *Nature*. 2016;529(7584):43-47.
10. Thomas F, Roche B, Ujvari B. Intrinsic versus Extrinsic Cancer Risks: The Debate Continues. *Trends Cancer*. 2016;2(2):68-69. Doi:10.1016/j.trecan.2016.01.004
11. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000;100(1):57-70.
12. Armitage P, Doll R. A two-stage theory of carcinogenesis in relation to the age distribution of human cancer. *Br J Cancer*. 1957;11(2):161-9.
13. Amosite asbestos and mesothelioma. *Lancet*. 1981; 2(8260-61):1397-1398.
14. Meng C, Bai C, Brown TD, et al. Human Gut Microbiota and Gastrointestinal Cancer. *Genomics Proteomics Bioinformatics*. 2018;16(1):33-49.
15. IARC monographs on the identification of carcinogenic hazards to humans https://monographs.iarc.who.int/list-of-classifications/. Last accessed 30 Oct 2022.
16. Kusiak RA, Springer J, Ritchie AC, et al. Carcinoma of the lung in Ontario gold miners: possible aetiological factors. *Br J Ind Med*. 1991;48(12):808-817.
17. Pearlman R, Frankel WL, Swanson B, et al. Prevalence and Spectrum of Germline Cancer Susceptibility Gene Mutations Among Patients With Early-Onset Colorectal Cancer. *JAMA Oncol*. 2017;3(4):464-471.
18. Tindle HA, Stevenson Duncan M, Greevy RA, et al. Lifetime Smoking History and Risk of Lung Cancer: Results From the Framingham Heart Study. *J Natl Cancer Inst.* 2018;110(11):1201-1207.
19. Hueper WC, Wiley F, Wolfe HD. Experimental production of bladder tumors in dogs by administration of beta-naphthylamine. *J Ind Hyg Toxicol.* 20:46-84 (1938).
20. Case RA, Hosker ME, McDonald DB, Pearson JT. Tumours of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry. I. The role

of aniline, benzidine, alpha-naphthylamine, and beta-naphthylamine. *Br J Ind Med*. 1954;11(2): 75-104.
21. Vineis P, Pirastu R. Aromatic amines and cancer. *Cancer Causes Control*. 1997;8(3):346-355.
22. Case RA. Tumours of the urinary tract as an occupational disease in several industries. *Ann R Coll Surg Engl*. 1966 Oct;39(4):213-35.
23. Xie C, Lu H, Nomura A, et al. Co-deleting Pten with Rb in retinal progenitor cells in mice results in fully penetrant bilateral retinoblastomas. *Mol Cancer*. 2015;14:93. Published 2015 Apr 24.
24. Draper GJ, Sanders BM, Brownbill PA, et al. Patterns of risk of hereditary retinoblastoma and applications to genetic counselling. *Br J Cancer*. 1992;66(1):211-219.
25. Ries LAG, Smith MA, Gurney JG, et al. Cancer incidence and survival among children and adolescents: United States SEER program 1975-1995. Bethesda, (MD): National Cancer Institute, SEER Program; 1999, p. 182.
26. Bassett JH, Forbes SA, Pannett AA, et al. Characterization of mutations in patients with multiple endocrine neoplasia type 1. *Am J Hum Genet*. 1998;62(2):232-244.
27. Marx SJ, Vinik AI, Santen RJ, et al. Multiple endocrine neoplasia type I: assessment of laboratory tests to screen for the gene in a large kindred. *Medicine (Baltimore)*. 1986;65(4):226-41.
28. McDonnell JE, Gild ML, Clifton-Bligh RJ, et al. Multiple endocrine neoplasia: an update. *Intern Med J*. 2019;49(8):954-961.
29. Bim LV, Navarro FCP, Valente FOF, et al. Retroposed copies of RET gene: a somatically acquired event in medullary thyroid carcinoma. *BMC Med Genomics*. 2019 Jul 9;12(1):104.
30. Czyz W, Morahan JM, Ebers GC, et al. Genetic, environmental and stochastic factors in monozygotic twin discordance with a focus on epigenetic differences. *BMC Med*. 2012Aug; 17;10:93.
31. Biwer C, Kawam B, Chapelle V, et al. The Role of Stochasticity in the Origin of Epigenetic Variation in Animal Populations. *Integr Comp Biol.* 2020 Dec 16;60(6):1544-1557.
32. Ushijima T, Watanabe N, Okochi E, et al. Fidelity of the methylation pattern and its variation in the genome. *Genome Res*. 2003;13(5):868-874.
33. Mai PL, Best AF, Peters JA, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. *Cancer*. 2016;122(23):3673-3681.
34. Schneider K, Zelley K, Nichols KE, Garber J. Li-Fraumeni Syndrome. In: Adam MP, Everman DB, Mirzaa GM, et al., eds. GeneReviews®. Seattle (WA): University of Washington, Seattle; January 19, 1999.
35. Werner H, Lapkina-Gendler L, Achlaug L, et al. Genome-Wide Profiling of Laron Syndrome Patients Identifies Novel Cancer Protection Pathways. *Cells*. 2019 Jun 15;8(6):596.
36. Benyi E, Linder M, Adami J, Kieler H, Palme M, Sävendahl L. Adult height is associated with risk of cancer and mortality in 5.5 million Swedish women and men. *J Epidemiol Community Health*. 2019 Aug;73(8):730-736.
37. Rafalko J, Kruglyak K, McCleary-Wheeler A et al. Age at cancer diagnosis by breed, weight, sex, and cancer type in a cohort of over 3,000 dogs: determining the optimal age to initiate cancer screening in canine patients. bioRxiv 2022.03.30.486448
38. Martineau D, Lemberger K, Dallaire A, et al. Cancer in wildlife, a case study: beluga from the St. Lawrence estuary, Québec, Canada. *Environ Health Perspect.* 2002 Mar;110(3):285-92.
39. Peto R, Roe FJ, Lee PN, et al. Cancer and ageing in mice and men. *Br J Cancer*. 1975 Oct;32(4):411-26.
40. Abegglen LM, Caulin AF, Chan A et al. Potential Mechanisms for Cancer Resistance in Elephants and Comparative Cellular Response to DNA Damage in Humans. *JAMA*. 2015 Nov 3;314(17):1850-60.
41. Ferlay J, Laversanne M, Ervik M, et al (2020). Global Cancer Observatory: Cancer Tomorrow. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/tomorrow, accessed October 15 2022.
42. Sulak M, Fong L, Mika K, et al. TP53 copy number expansion is associated with the evolution of increased body size and an enhanced DNA damage response in elephants. *Elife*. 2016 Sep 19;5:e11994.
43. Dunn GP, Bruce AT, Ikeda H, et al. Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol.* 2002 Nov;3(11):991-8.
44. Reynolds I, Healy P, Mcnamara DA. Malignant tumours of the small intestine. *Surgeon*. 2014;12(5):263-270.
45. Helander HF, Fändriks L. Surface area of the digestive tract – revisited. *Scand J Gastroenterol*. 2014;49(6): 681-689.
46. Wan Q, Zhao R, Xia L, et al. Inflammatory bowel disease and risk of gastric, small bowel and colorectal cancer: a meta-analysis of 26 observational studies. *J Cancer Res Clin Oncol*. 2021;147(4):1077-1087.
47. Neugut AI, Jacobson JS, Suh S, et al. The epidemiology of cancer of the small bowel. *Cancer Epidemiol Biomarkers Prev.* 1998;7(3):243-251.
48. Bray F, Colombet M, Mery L, et al. (2017). Cancer Incidence in Five Continents, Vol. XI (electronic version). Lyon: International Agency for Research on Cancer. Available at: https://ci5.iarc.fr
49. Sun S, Osterman MD, Li M. Tissue specificity of DNA damage response and tumorigenesis. *Cancer Biol Med.* 2019 Aug;16(3):396-414.
50. Blanpain C, Mohrin M, Sotiropoulou PA, et al. DNA-damage response in tissue-specific and cancer stem cells. *Cell Stem Cell.* 2011 Jan 7;8(1):16-29.
51. Haselkorn T, Whittemore AS, Lilienfeld DE. Incidence of small bowel cancer in the United States and worldwide: geographic, temporal, and racial differences. *Cancer Causes Control*. 2005;16(7):781-7.

52. Schrock AB, Devoe CE, McWilliams R, et al. Genomic Profiling of Small-Bowel Adenocarcinoma. *JAMA Oncol*. 2017;3(11):1546-1553.
53. Boffetta P, Farioli A, Rizzello E. Application of epidemiological findings to individuals. *Med Lav.* 2020; 111(1):10-21.
54. Li Y, Liang M, Mao L, et al. Robust estimation and variable selection for the accelerated failure time model. *Stat Med.* 2021;40(20):4473-4491.
55. Stanta G, Campagner L, Cavallieri F, et al. Cancer of the oldest old. What we have learned from autopsy studies. *Clin Geriatr Med.* 1997 Feb;13(1):55-68.
56. Saltzstein SL, Behling CA, Baergen RN. Features of cancer in nonagenarians and centenarians. *J Am Geriatr Soc.* 1998 Aug;46(8):994-8.
57. Andersen SL, Terry DF, Wilcox MA, et al. Cancer in the oldest old. *Mech Ageing Dev*. 2005;126(2):263-7.
58. Arbeev K, Ukraintseva S, Arbeeva LS, et al. 2005. Decline in Human Cancer Incidence Rates at Old Ages: Age-Period-Cohort Considerations, Demographic Research, Max Planck Institute for Demographic Research, Rostock, Germany, 2005;12(11):273-300.
59. Harding C, Pompei F, Lee EE, Wilson R. Cancer suppression at old age. *Cancer Res.* 2008 Jun 1;68(11): 4465-78.
60. Hashim D, Carioli G, Malvezzi M, et al. Cancer mortality in the oldest old: a global overview. *Aging (Albany NY).* 2020 Sep 3;12(17):16744-16758.
61. Siu AL. US Preventive Services Task Force. Screening for Breast Cancer: US Preventive Services Task Force Recommendation Statement [published correction appears in Ann Intern Med. 2016 Mar 15;164(6):448]. *Ann Intern Med.* 2016;164(4):279-296.
62. Davidson KW, Barry MJ, Mangione CM, et al. US Preventive Services Task Force. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2021;325(19):1965-1977.
63. Curry SJ, Krist AH, Owens DK, et al. US Preventive Services Task Force. Screening for cervical cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2018;320(7):674-686.
64. Lee EH, Han MA, Lee HY, et al. Liver cancer screening in Korea: a report on the 2008 National Cancer Screening Programme. *Asian Pac J Cancer Prev.* 2010;11(5): 1305-1310.
65. Setoyama H, Tanaka Y, Kanto T. Seamless support from screening to anti-HCV treatment and HCC/ decompensated cirrhosis: Subsidy programs for HCV elimination. *Glob Health Med.* 2021;3(5):335-342.
66. Hoffman RM, Sanchez R. Lung Cancer Screening. *Med Clin North Am.* 2017;101(4):769-785.
67. Wood DE, Kazerooni EA, Baum SL, et al. Lung Cancer Screening, Version 3.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2018; 16(4):412-441.
68. Krist AH, Davidson KW, Mangione CM, et al. US Preventive Services Task Force. Screening for lung cancer: US Preventive Services Task Force recommendation statement. *JAMA.* 2021;325(10):962-970.
69. Leja M, Grinberga-Derica I, Bilgilier C, et al. Review: Epidemiology of Helicobacter pylori infection. *Helicobacter*. 2019;24(Suppl 1):e12635.
70. Fuccio L, Zagari RM, Eusebi LH,et al. Meta-analysis: can Helicobacter pylori eradication treatment reduce the risk for gastric cancer? *Ann. Intern. Med.* 2009; 151:121-128.
71. Liou JM, Malfertheiner P, Lee YC, et al. Screening and eradication of Helicobacter pylori for gastric cancer prevention: the Taipei global consensus. *Gut*. 2020;69(12): 2093-2112.

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Welder's lung and brain MRI findings in manganese-exposed welders

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Keywords: Welders' lung; pneumoconiosis; manganism; T1 hyperintensity; blood manganese levels

Abstract

Background: *Biomarkers of manganese (Mn) exposure and manganism are poorly understood. Blood Mn levels are often used to assess exposure, while brain Mn accumulation may be demonstrated by pallidal hyperintensity at magnetic resonance imaging (MRI). Mn-containing electrodes used in manual metal arc welding may be associated with the welder's lungs.* **Methods:** *A cross-sectional study was set up to compare T1 intensity in basal ganglia at MRI and Mn blood levels in subjects with or without pneumoconiosis. Clinical, radiological, pulmonary function and laboratory parameters were assessed among 154 welders referred to our hospital for suspected pulmonary pathology.* **Results:** *The study group included 123 male welders with pneumoconiosis (79.9%) and 31 welders without pulmonary damage (20.1%). The cases without pneumoconiosis were younger (38.5±6.6 vs 42.1±7.1, p=0.012). Cases with pneumoconiosis had blood lower Mn levels [13.5 (10-21)] as compared to those without pneumoconiosis [18.5 (7.8-34)], p=0.035. In the same groups, the cases with high blood Mn levels were 49 (39.8%) and 18 (58.1%) p=0.052, respectively. Brain MRI hyperintensity was found in 86 (55.8%) subjects with welder's lung 63 (51.2%) but also in 23 (74.2%) individuals without welder's lung. MRI hyperintensity in basal ganglia was significantly related to high blood Mn (p<0.005).* **Conclusion:** *This is the first study evaluating blood Mn levels of welders and their correlation with pulmonary and neurological effects. In Mn-exposed welders, poor working conditions may be associated with exposure fibrogenic fumes leading to chronic lung diseases and hyperintensity in brain MRI suggesting Mn accumulation.*

1. Introduction

Welding is a process of joining metal parts by heating or pressure, and welders work in many branches of industry [1]. According to the US Bureau of Labor Statistics, the number of welders worldwide is estimated to exceed one million. In the USA in 1988, there were 500,000 welders. In 2019 there were still 438,900 welders [2]. In our country, welding is done in 6,417 workplaces, but the number of welders is unknown [3].

Manual metal arc is the most common welding technique, resulting in significant respiratory exposure to complex mixtures of toxic fumes, vapors, and gases containing many hazardous chemical agents (ozone, carbon monoxide, nitrogen oxides and metallic elements) [4]. At high temperatures, metallic particles are oxidized. Generally, oxides of metals in

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the form of condensed particles such as iron, chromium, nickel, Mn, and aluminum occur [5]. Typically, the welder should only watch the process at a distance of 50 centimeters and can inhale welding fumes [6]. Exposure varies according to the type of welding and metallic composition of bars, ventilation of the working environment, and characteristics of the protective equipment [4].

Potential adverse health effects include siderosis, pneumoconiosis, metal fume pneumonia, interstitial fibrosis, bronchitis, and Mn poisoning, e.g., neurological, and respiratory changes associated with manganism [7-9]. The welder's lung is a disease that affects the respiratory tract at all levels and parenchyma together following inhalation of welding fumes [10, 11].

Exposure to welding fumes mainly occurs using steel (Mild Steel - MS and Stainless Steel - SS) or carbon steel materials and usually contain Fe (80-95%) and Mn (1-15%) [12]. After inhalation, the absorbed Mn is transported in the blood and crosses the blood-brain barrier (BBB) via specific carriers, selectively accumulating in comparison with other tissues. Mn exposure has been shown to induce a neurological syndrome that resembles Parkinson's disease [13]. The selectivity of Mn accumulation in the basal ganglia has yet to be fully delineated. Several studies showed that an Mn transporter (divalent metal transporter 1-DMT1) is highly expressed in the basal ganglia. Mn promotes neurotoxicity fueling ROS production and causing oxidative stress, thereby impairing mitochondrial enzyme activity and energy production [14]. Elevated blood Mn level is associated with T1 hyperintensity in the basal ganglia at MRI as a biological marker of Mn accumulation. However, T1 hyperintensity in basal ganglia can occur with blood Mn levels within the reference range. Thus, T1 hyperintensity in welders has been recognized as a sign of chronic Mn exposure, a marker of brain Mn accumulation [15-17].

Pathologies that may develop in the lung after inhalation of heavy metals and other toxic or fibrogenic materials in welding fumes are well known. This study aims to assess and compare the blood Mn levels and the resulting central nervous system (CNS) involvement in cases with or without welder's lung. We hypothesized that welding-related Mn exposure would be related to pulmonary and neurological damage and relation with blood Mn levels, and T1 hyperintensity in basal ganglia would be a marker of this damage.

2. Methods

2.1. Study design

This study is a retrospective cross-sectional study conducted in Ankara Occupational and Environmental Diseases Hospital. We accepted consecutive welders exposed to Mn who have admitted to our hospital between January 2015 and August 2019. We used the data of the digital archive system. We retrospectively analyzed clinical, radiological, lung functional characteristics, and laboratory parameters of welders referred to our hospital by occupational physicians suspecting a pulmonary disease. The study group consisted of 154 male welders with welders' lung disease (n=123; 79.9%) and welders without pulmonary parenchymal damage (n=31; 20.1%) employed in steel fabrication factories around our city. Welders used at least one of the following processes: manual arc welding with a covered electrode (MMA), semi-automatic gas-shielded bare wire metal arc welding (MIG-MAG), and manual arc welding with a non-consumable tungsten electrode under inert as shielding (TIG). All subjects were evaluated by a pneumologist, an occupational health physician, and a neurologist. According to the workplace occupational health and safety management reports, all workers had a history of exposure to one or more occupational risk factors in this production process. The managements did not provide ambient measurements because of administrative restrictions in the workplaces.

2.2. Neurological evaluation

Two independent neurologists, blinded to other clinical or laboratory data, performed a neurological examination and a T1 hyperintensity assessment. Globus pallidus was examined in a T1-weighted axial section. Patients considered positive by

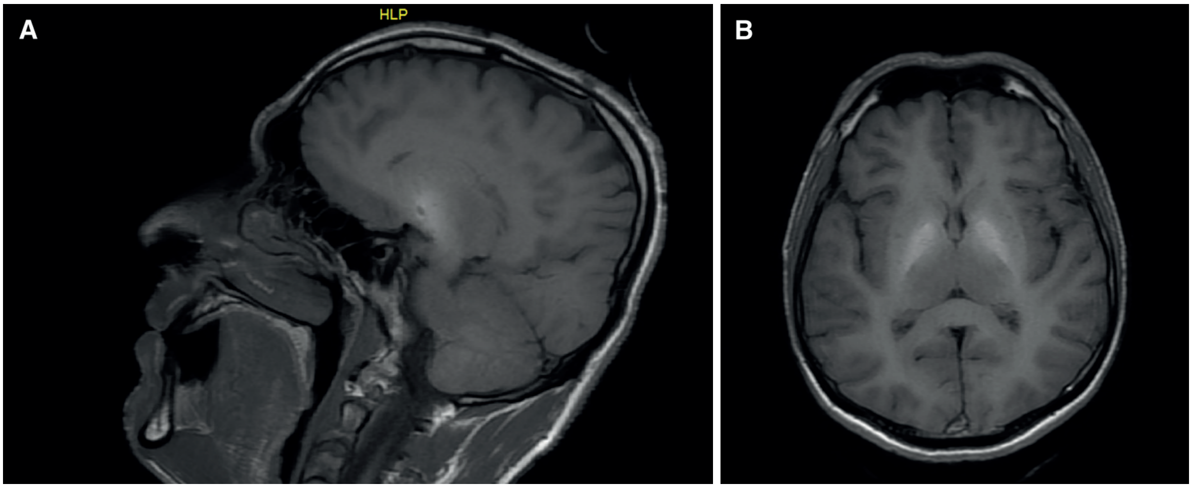

Figure 1. (A and B). MRI sagittal (A) and axial (B) image of a Mn-exposed welder with TW1 hyperintensity.

both neurologists were classified as T1 hyperintensity positive (Figure 1A and 1B). Brain MRI was performed using a 1.5 Tesla system (Ingenia model no: 7813-72; Philips Medical Systems, The Netherlands, Tilburg).

2.3. Pulmonary function assessment

Tests were performed following the American Thoracic Society (ATS) criteria [18]. A standard spirometry measurement was done using dry-seal-spirometry (Zan 100, nSpire Health Inc., Oberthulba, Germany).

2.4. Radiological assessment

Posteroanterior (PA) chest X-rays were taken. A short exposure time with a high voltage technique was used (Trophy UFXRAY, 500 mA, TM). PA chest X-rays were evaluated following International Labour Organization (ILO) 2011 standards [19] and graded by three readers (two chest disease specialists and a radiologist). According to the ILO classification, the ones with profusion 0/1, 1/0, 1/1 and 1/2 have been classified as category 1; the ones with profusion 2/1, 2/2 and 2/3 have been classified as category 2; and the ones with profusion 3/2, 3/3 and 3/+ have been classified as category 3. All subjects whose X-rays with suspect anomalies underwent thoracic high-resolution computed tomography (HRCT). Slices in 1 mm size at 1.5 s intervals which increased by 10 mm with a high-resolution algorithm, were used.

2.5. Blood manganese (Mn) assessment

Blood samples were collected before work shifts and outside the working facilities on Monday (at the beginning of a work week). Inductively-Coupled Plasma-Mass Spectroscopy (ICP-MS) (Agilent 7700X, USA) was used for the analysis of metals in collected samples. Plasma torch argon purity was higher than 99.999%. The method was validated by analysis of certified reference materials (Seronorm Trace Elements, Billingstad, Norway). The detection limit for whole blood Mn levels was 18 ng/ml.

2.6. Statistical analysis

The statistical evaluations have been conducted by computer, using the PASW Statistics for Windows SPSS, Version 21.0 (SPSS Inc, Chicago, IL, USA) package program. Kolmogorov-Smirnov test was used to analyze consistency to normal distribution. Values are presented as median (interquartile range) or mean±SD. The Student's t-test was used for continuous variables, and the Mann-Whitney U test for non-parametric variables to determine the difference between pneumoconiosis and controls.

The chi-Squared test was used to analyze categorical variables. Spearman's test was performed for correlation analysis.

3. Results

A total of 154 welders, 123 (79.9%) cases with Pneumoconiosis and 31 (20.1%) welders without pulmonary parenchymal damage were included in the study. All welders were male; their mean age was 41.4±7.2 (min-max=27-60). Smoking pack years median was 12 (25-75 percentiles=6-20) and duration of exposure was 187.7±74.8 (min-max= 24-384). All of the welders were working without respiratory protection in a non-ventilated space. Clinical data of all workers and workers with or without pneumoconiosis are given in Table 1.

The evaluation of PA chest X-rays according to ILO classification is shown in Table 2. Sixteen (13%) cases were evaluated as category two and above, and large opacity was detected in 2 (1.6%) patients. In HRCT micronodules (n=122, 99.2%), reticular opacities (n=74, 60.2%), lymphadenopathy (n=13, 10.6%), conglomerate masses (n=4, 3.3%), and emphysema (n=21, 17.1%) are detected in patients with pulmonary damage.

The cases without pneumoconiosis were younger (42.1±7.1 vs 38.5±6.6 p=0.012). In patients with pneumoconiosis, the number of smokers was higher than in subjects with normal pulmonary parenchyma: n=112(91.1%) vs n=21(67.7%) p=0.002. Blood Mn levels were higher in cases without pneumoconiosis: 18.5 (7.8-34) as compared to 13.5 (10-21) in patients with welder's lung, p=0.035; likewise, there were more cases with high blood Mn levels: 18 (58.1%) vs 49 (39.8%), p=0.052, in subjects with and without pneumoconiosis, respectively. Brain MRI showed hyperintensity in 86 (55.8%) cases exposed to welding fumes. They all had motor symptoms, like tremors and painful limb spasms, and non-motor symptoms, like dementia and memory loss. Hyperintensity of basal ganglia was observed and higher in individuals without welders' lung: 63 (51.2) vs 23 (74.2) p=0.017. The presence of hyperintensity in basal ganglia was related to the high blood Mn level (p<0.005). When all exposed cases were evaluated,

Table 1. Sociodemographic and clinical data of all welders, and with or without pneumoconiosis.

			Pneumoconiosis		
		All cases	**Yes**	**No**	**p**
Number of patients		154	123	31	-
Age (mean±SD, min-max)		41.4±7.2 (27-60)	42.1±7.1 (27-60)	38.5±6.6 (27-51)	0.012*
Smoking status, n (%)	*Non/ ex smoker*	21 (13.6)	11 (8.9)	10 (32.3)	0.002**
	Active smoker	133 (86.4)	112 (91.1)	21 (67.7)	
Pack years, median (25-75 percentiles)		12 (6-20)	12 (6.25-20)	10 (5-17)	ns†
Exposure time (Mo.), mean±SD (min-max)		19±5 (24-384)	192±76 (48-384)	173±68.8 (24-360)	ns*
Blood Mn (µg/l), median (25-75 perc.)		14,8 (10.9-21)	13.5 (10-21)	18.5 (7.8- 34)	0.035†
High blood Mn, n (%)		67 (43.5)	49 (39.8)	18 (58.1)	0.052**
Basal ganglia hyperintensity, n (%)		86 (55.8)	63 (51.2)	23 (74.2)	0.017**
FEV1 (% predicted±SD)		93.7±14,3	91.8±14,1	97.8±14.4	0.037*
FVC (% predicted±SD)		94.3±14.5	93.1±14.3	99.2±14.6	0.037*
FEV1/FVC (%±SD)		81.6±7,1	81.6±7.4	81.4±6.1	ns*
MEF25-75 (% predicted±SD)		79.1±14.9	78.3±14.1	82.1±17.8	ns*

Mn: manganese ns: not significant
High blood Mn level > 18 ng/ml.
**Indepedent sample T- test.*
***Chi squared test.*
†Mann Whitney U Test.

Table 2. PA chest X-ray of cases with Pneumoconiosis (type and frequency of radiological pattern).

Pattern	Shape and frequency	n=123 (100%)
Small opacity	p	100 (81.4)
	q	21 (17)
	r	1 (0.8)
	s	1 (0.8)
	t	-
	u	-
Profusion	1/0	50 (40.7)
	1/1	45 (36.6)
	1/2	12 (9.8)
	2/1	4 (3.3)
	2/2	6 (4.9)
	2/3	2 (1.6)
	3/3	4 (3.3)
Large Opacity		
	A Opacity	2 (1.6)
	B Opacity	-
	C Opacity	-
Pleural abnormalities		4 (3.3)

blood Mn levels were higher in patients with hyperintense basal ganglia than those without (12.3±5.3 and 19.4±6.8 $p<0.05$).

Among welders with pneumoconiosis, high blood Mn levels occurred more frequently in welders with T1 hyperintensity ($p<0.005$), but no correlation was observed between blood Mn levels and radiological profusion ($p=0.902$).

4. Discussion

In our study, we present the effects of welding fumes on different systems when protective measures are not taken in cases and exposed to welding fumes in primitive working conditions with inadequate ventilation or protection. The most important clinically relevant findings of this study were that the pulmonary system is affected by exposure to welding fumes via inhalation, and the central nervous system is affected by the systemic route. In chronic processes, transition elements such as Mn and fibrogenic materials can accumulate in different tissues and cause damage to other systems. While welder's lung was detected in 123 (79.8%) and Mn accumulation in the globus pallidus in 86 (55.8%) cases of 154 welders exposed to welding fumes, high blood Mn levels were observed in only 67 (43.5%) of all welders. Moreover, the number of subjects with high blood Mn levels was higher among patients without pneumoconiosis. Also, the number of patients with T1 hyperintensity was higher in cases without pneumoconiosis. It should be noted that Mn accumulation in the globus pallidus occurred in 23 (26.7 %) patients without pulmonary damage. In contrast, occupational health physicians focus more on the pulmonary effects of welding fumes than the neurological effects of Mn brain accumulation.

The development of welders' lung disease or pneumoconiosis follows combined exposure to metal fumes and fibrogenic substances such as silica, coal or asbestos in the working environment [20]. In animal studies, fibrosis has been shown with very high doses and long-term exposure to welding fumes, and Buerke et al. detected interstitial fibrosis in electron microscopy examination of CT and biopsy materials of welders who had been exposed to high levels of welding fumes for many years [9] [21]. In our study, welder's lung was detected in 123 (79.8%) cases, and no difference was found between the cases with and without pneumoconiosis in terms of exposure time and smoking pack year ($p>0.005$).

Blood is still recommended as a suitable biological medium for the biomonitoring of Mn exposure, whereas other media (nails, stools, urine) are not. It had been suggested that blood Mn might be helpful as a biomarker for identifying new exposures by inhalation [22]. However, blood Mn concentrations are not as reliable as iron in the past or long-term exposures [23]. Since the blood Mn level is an indicator of short-term exposure, this may be why it is not increased in almost half of the cases with both lung and brain involvement.

Symptoms such as sleep disturbance, headache, mood disorder and EEG disturbances can be observed after exposure to Mn [24]. High-dose and chronic exposure to welding fumes, hence Mn, can lead to the clinical condition resulting in neurological damage called manganism, which causes a range of symptoms resembling Idiopathic Parkinson's Disease [25]. Distinguishing manganism and Idiopathic Parkinson's Disease are challenging, especially in the advanced stages. Both occur with the degeneration of cells in the basal ganglia, which is the center of fine and coordinated movements. In manganism, T1 hyperintensity is seen in brain MRI by deposition of Mn in the globus pallidus in the basal ganglia. T1 hyperintensity in globus pallidus before the high blood Mn levels or Mn toxic effects indicates chronic Mn exposure. It is recommended for use as a biological marker [26, 27]. In our study, hyperintensity in basal ganglia was associated with high blood Mn levels in cases with welder's lungs ($p=0.005$). Still, in welders without pulmonary pathology, there was no difference in blood Mn levels between welders with hyperintense basal ganglia and welders without CNS pathology ($p=0.170$).

The lack of exposure assessment and environmental monitoring, the lack of data on the Pallidal Index and the cross-sectional design were limitations of this study. Also, welders can be exposed to many toxic and fibrogenic particulate matters, not only to Mn. The strength of this study is the concurrent assessment of lung and brain effects associated with exposure to welding fumes and the availability of individual biomonitoring data. However, blood Mn levels are less than ideal biomarkers of recent exposure or accumulation.

5. Conclusions

To our knowledge, this is the first study evaluating blood Mn levels of welders with pulmonary and neurological effects of welding fumes. In summary, our results indicate that Mn and fibrogenic materials exposure resulting from welding fume exposure in poor working conditions may be associated with chronic lung diseases, hyperintensity in brain MRI and Parkinson-like diseases due to accumulation of Mn. Our core message is to improve the awareness of this occupational threat in welding process and the importance of close neurological follow-up of patients diagnosed with welders' lung should be emphasized. Also, for future study design, neurological evaluation and biological monitoring will be added to the follow-up study to evaluate chronic effects of metal exposure.

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Declaration of Interest: The authors declare no conflict of interest.

References

1. ILO Encyclopaedia of occupational health and safety, 4th edition (2011). Welding and thermal cutting. Available from: https://www.iloencyclopaedia.org/component/k2/item/676-welding-and-thermal-cutting. Accessed December 2021.
2. US Bureau of Labor Statistics. Available from: https://www.bls.gov/ooh/production/welders-cutters-solderers-and-brazers.htm. Accessed December 2020.
3. Esnaf ve Sanatkâr İstatistikleri Bülteni T.C. Gümrük ve Ticaret Bakanlığı Esnaf ve Sanatkârlar Genel Müdürlüğü 2014. Available at esnaf.gtb.gov.tr/data/53fdcc9ef29370a0e461fadf/Temmuz_2014.pdf. Accessed December 2020.
4. Antonini JM, Lewis AB, Roberts JR, Whaley DA. Pulmonary effects of welding fumes: review of worker and experimental animal studies. *Am J Ind Med*. 2003; Apr;43(4):350-60. Doi: 10.1002/ajim.10194. PMID: 12645092
5. Howden DG, Desmeules MJA, Saracci R, Sprince NL, Herber PI. Respiratory hazards of welding: Occupational exposure characterization. *Am Rev Respir Dis*. 1988;138:1047-1048.
6. Beckett WS. Metal industry and related jobs (including welding). In Occupational and Environmental Lung Diseases Ed Tarlo SM, Cullinan P, Nemery B. 2010, John Wiley & Sons.
7. American Welding Society (AWS) Safety and Health Committee. Effects of welding on health. XIV:2011.550 NW (US). Available from: https://www.aws.org/standards/page/effects-of-welding-on-health. Accessed December 2021.
8. Billings CG, Howard P. Occupational siderosis and welders' lung: a review. *Monaldi Arch Chest Dis*. 1993; 48:304-314.
9. Buerke U, Schneider J, Rosler J, Woitowitz HJ. Interstitial pulmonary fibrosis after severe exposure to welding fumes. *Am J Ind Med*. 2002;41(4): 259-268.
10. Kalliomäki PL, Sutinen S, Kelhä V, Lakomaa E, Sortti V, Sutinen S. Amount and distribution of fume

contaminants in the lungs of an arc welder post mortem. *Br J Ind Med*. 1979;Aug;36(3):224-30. Doi: 10.1136/oem.36.3.224. PMID: 500782; PMCID: PMC1008569
11. Şimşek C. Kaynakçı Akciğeri Türkiye Klinikleri, Tıp Bilimleri 1992;12:212-8.
12. Taube F. Manganese in occupational arc welding fumes-aspects on physiochemical properties, with focus on solubility. *Ann Occup Hyg*. 2013;Jan;57(1):6-25. Doi: 10.1093/annhyg/mes053. Epub 2012 Sep 20. PMID: 22997412
13. Defazio G, Soleo L, Zefferino R, Livea P. Manganese-toxicity inserumlessdissociated mesencephalic and striatal primary cultures. *Brain Res. Bull*. 1996;40:257.
14. Wolff NA, Garrick MD, Zhao L, Garrick LM, Ghio AJ, Thevenod F. A role for divalent metal transporter (DMT1) in mitochondrial uptake of iron and manganese. *Sci Rep.* 2018;8:211. Doi: 10.1038/s41598-017-18584-4
15. Dorman DC, Struve MF, Marshall MW, Parkinson CU, James RA, Wong BA. Tissue manganese concentrations in young male rhesus monkeys following subchronic manganese sulfate inhalation. *Toxicol Sci*. 2006;92:201-210.
16. Kim Y, Kim KS, Yang JS, et al. Increase in signal intensities on T1-weighted magnetic resonance images in asymptomatic manganese-exposed workers. *Neurotoxicology*. 1999;20:901-907.
17. Li SJ, Jiang L, Fu X, et al. Pallidal index as biomarker of manganese brain accumulation and associated with manganese levels in blood: a meta-analysis. *PLoS One*. 2014;9:e93900.
18. American Thoracic Society. Standardization of Spirometry, 1994 update. *Am J Respir Crit Care Med*. 1995;152(3):1107-36. Doi: http://dx.doi.org/10.1164/ajrccm.152.3.7663792
19. International Labour Office. Guidelines for the use of the ILO International Classification of Radiographs of Pneumoconioses. ILO Occupational Safety and Health Series No. 22. Revised edition. Geneva: ILO; 2011. pp. 1-11.
20. Morgan WKC. Arc welders' lung complications by conglomeration. *Am Rev Respir Dis*. 1962;85:570-575.
21. Yu IJ, Song KS, Chang HK, et al. Lung fibrosis in Sprague-Dawley rats, induced by exposure to manual metal arc-stainless steel welding fumes. *Toxicol Sci*. 2001;63(1):99-106.
22. Wongwit W, Kaewkungwal J, Chantachum Y, Visesmanee V. Comparison of biological specimens for manganese determination among highly exposed welders. *Southeast Asian J Trop Med Public Health.* 2004; 35(3):764-769.
23. Lu L, Zhang LL, Li GJ, Guo W, Liang W, Zheng W. Alteration of serum concentrations of manganese, iron, ferritin, and transferrin receptor following exposure to welding fumes among career welders. *Neurotoxicology*. 2005;Mar;26(2):257-65. Doi: 10.1016/j.neuro.2004.09.001. PMID: 15713346; PMCID: PMC4002285: s.n.
24. Halatek T, Sinczuk-Walczak H, Szymczak M, Rydzynski K. Neurological and respiratory symptoms in shipyard welders exposed to manganese. *Int J Occup Med Environ Health*. 2005;18(3): 265-274.
25. Racette BA, Mcgee-Minnich L, Moerlein S, Mink J, Videen T, Perlmutter JS. Welding-related parkinsonism: Clinical features, treatment, and pathophysiology. *Neurology*. 2001;56(1):8-13.
26. Kim Y. High signal intensities on T1-weighted MRI as a biomarker of exposure to manganese. *Ind Health*. 42(2):111-115, 2004.
27. Olanow CW. Manganese-induced parkinsonism and Parkinson's disease. *Ann NY Acad Sci*. 2004; 1012:209–223.

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Contribution to validation of the Italian version of work ability personal radar

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Abstract

Background: *Work ability (WA) is an important construct in Occupational Health. Over the years, various WA detection tools have been developed, and a new one is the Work Ability Personal Radar (WA-PR), capable of investigating all the dimensions that define the complexity of WA. In this new version, not only the physical dimensions are considered but also the psycho-social aspects of work capable of impacting WA. The WA-PR was born in the Finnish context. However, recently, it has also been validated elsewhere. In light of the literature on WA assessment tools, our goal is to contribute to validating the WA-PR in the Italian context.* **Methods:** *Data were collected using a self-reported questionnaire administered to 405 workers in the chemical industrial sector.* **Results:** *Results show that the WA-PR correlate with WAI and other constructs conceptually related to work ability: the need for recovery, stress, and general health.* **Conclusions:** *Data analysis confirms that the WA-PR is a valuable and reliable tool for evaluating work ability in the Italian context.*

1. Introduction

1.1. The concept of work ability and measurement tools

Work ability (WA) is an important construct in the occupational health field, both in practice and research. It was initially defined as a person's physical and mental ability to meet the demands of their job [1]. Initially, the definition of WA was theoretical, but theorization has become complex over time. Recently, some authors have inserted the concept of WA into the job demand-resources model (JDR model) [2], which conceptualizes how well-being at work is available from questions and resources.

Studies show that WA influences work outcomes such as job attitude (satisfaction, commitment), performance, strain (burnout, fatigue), motivation and withdrawal behavior. This theorization would explain the results of some WA studies, highlighting its impact on well-being/malaise at work [3-7]. Furthermore, this theory confirms the centrality and the importance of investigating WA and planning interventions [8].

To detect the construct of WA, in the 1980s, the Finnish Institute of Occupational Health (FIOH) invented the Work Ability Index (WAI), which

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has been translated into 26 languages and is used worldwide [3].

The WAI consists of seven components that constitute individual work ability:

- WAI 1: Current work ability compared with lifetime best (1 item);
- WAI 2: Work ability to job demands (2 items);
- WAI 3: Current diseases diagnosed by a physician (14 disease groups);
- WAI 4: Estimated work impairment due to diseases (1 item);
- WAI 5: Sick leave during the past year (1 item);
- WAI 6: Prognosis of work ability two years from now (1 item);
- WAI 7: Mental resources (3 items).

These seven components are summed, with a total score being classified as poor WA (7-27), moderate WA (28-36), good WA (37-43) or excellent WA (44-49). The cut-off values were derived from the 15th and 85th percentile of the population in 1981 investigated in the first WAI study on municipal workers in Finland [9, 10]. These values have remained unchanged over time.

Some authors have made some criticisms of the WAI: (i) The WAI does not comprehensively cover the concept of work ability, and it focuses too much on health aspects (especially medical diagnosis) [10, 11]; (ii) The WAI combines objective health indicators and perceptual assessments of WA into a unique score [3, 12]. In this direction, several studies identified two or three factors included in the WAI and not only one [12-19]; (iii) The WAI includes scores using different response formats (for example, 0-5 or 0-10), but the scores are summed and converted into ordinal categories. In terms of psychometric proprieties, this is problematic [3]; (iv) The WAI is often administered in different ways (interview with the medical doctor during the visit, self-report questionnaire, etc.) [10]; (v) The WAI is too long, taking about 15 minutes to complete [8, 20].

New tools have recently been developed to evaluate WA from a more holistic and subjective perspective [21]. For example, in the literature, the first WAI item is often used as an indicator of subjective WA (the single item measuring work ability with reference to best in lifetime), and it is often called Work Ability Score (WAS) [10, 11, 22]. However, using a single item removes the objective health component of WAI and increases measurement error due to the bias inherent in the respondent's self-assessments [3, 23].

Another solution adopted in the literature to evaluate the subjective dimension of WA is using Item 2 of the WAI in relation to both mental and physical work demands [10, 24-26]. However, some authors criticize the use of Item 2 of the WAI because this item does not capture the organizational factors but only the mental and physical job demands [27].

Another solution to assess WA is the use of some items of the WAI plus one or two additional questions; for instance, Palermo et al. [28] used four items to evaluate WA: two from the WAI and two new ones (their expected WA five and ten years in the future). McGonagle et al. [29] used the first three items of the WAI plus one new item (current WA in relation to social skill demands). Some authors even used six items of the WAI (excluding item 3; for example, the WAI-R) [30].

A new instrument for evaluating WA is Work Ability Personal Radar (WA-PR) [21], which is based on a more comprehensive approach to assessing WA [3]. In this questionnaire, contextual factors are included in the measure of WA. More specifically, the questionnaire refers quite faithfully to the multidimensional model of the WA house [31, 32]. In the house model, the four floors of the house and its nearby environment represent five interrelated dimensions that underlie work ability. Together, the three bottom floors of the house represent "individual's resources" that affect work ability, the fourth floor is conceived of as the "work factor", and the context in which the house is placed is "context life" (Figure 1) [21]: (i) HF: The first-floor concerns health and functional capacity, which are fundamental to WA, and the literature has often emphasized the relationship between physical health and WA; (ii) CO: the second floor of the house illustrates occupational competence consisting of work ability-related expertise, knowledge and skills. Without any skills acquired by experience or training, coping with the job would not be possible;

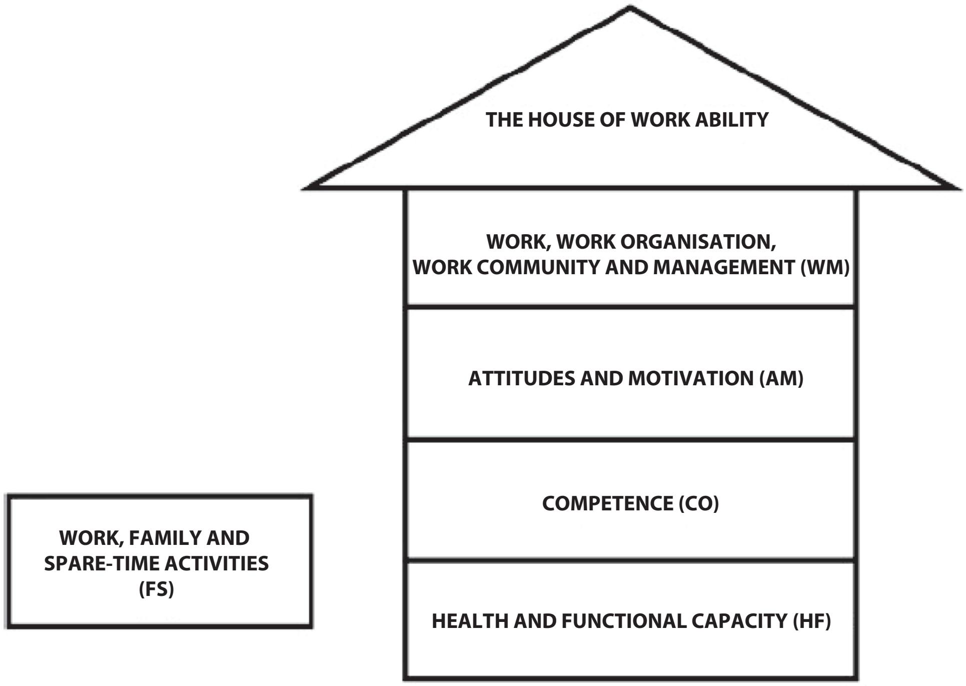

Figure 1. The structures of the house of work ability.

(iii) AM: The third floor of the house consists of attitudes and motivations that represent attitudinal factors affecting work ability; (iv) WM: The fourth floor of the house consists of working conditions, work organization, work community and management. This floor has an inevitable effect on a person's ability to work. One way to comprehend work ability within the house model is to examine the balance between personal resources (first three floors) and the demands of the work (fourth floor) [31]. If there is a balance between resources and work demands, the WA is good; conversely, the ability to work will decline if resources are insufficient to deal with demands. Similar conceptualizations of WA have also been presented in occupational health literature, especially the JD-R model [33]. According to the JD-R model, every job consists of (a) Job demands requiring sustained effort and cost (psychological or physical), thereby increasing strain and decreasing motivation; (b) Job resources aiding in accomplishing work goals, thus reducing job demands and increasing motivation and buffering the adverse effects of job demands. Brady et al. [3] argue that the JD-R model offers a valuable framework for investigating the antecedent and outcome of WA: they insert the WA construct like a moderator into the JD-R model, where WA is influenced positively by job and personal resources and negatively by job demands. Similarly, WA affects some outcome variables (e.g. performance, strain, exit intention); (v) FS: the nearby environment and societal surroundings are also incorporated in the house model of work ability and constitute the fifth floor.

All five dimensions are interrelated and dependent on one another (32). There is a feedback cycle and reciprocated causation between the structures.

In this theoretical framework, the WA-PR provides a method for measuring subjective experiences of WA according to the dimensions depicted in the house model. The objective is to achieve versatile assessments based on which more accurate allocations of interventions and promotions of WA may be executed [21].

1.2. Aims of the study

In light of this literature on WA assessment tools, our goal is to contribute to the validation of the

WA-PR in the Italian context. More specifically: (i) we explore the associations between the WAI and the WPWI, WAE and WWI, respectively. Moreover, we examine whether the WPWI, WAE, WWI and WAI correlate with psychological health (i.e., need for recovery, stress level, general health) and physical well-being (i.e., pharmacological therapy, presence of diseases diagnosed by the doctor during health surveillance, back pain and visual disorders); (ii) we explore the psychometric properties of WA-PR.

2. Methods

The sample comprises 405 workers in the chemical industrial sector employed by a production plant in the North of Italy. The survey was conducted in February and March 2019 within a project aimed at assessing the quality of life considering aging at work. The data were collected using a self-reported questionnaire in the presence of researchers, and all subjects were informed about the study's aims. The questionnaire was distributed to the entire staff of the plant, consisting of 450 workers (response rate: 90%). The workers' participation was entirely voluntary, and the research group ensured anonymity in the data collection at the Department of Psychology of the University of Turin. The research conformed to the Declaration of Helsinki. No treatment, including medical treatment, invasive diagnostics or procedures causing psychological or social discomfort, was administered to the participants. Moreover, the contents of the questionnaires were previously approved by the management and security officers of the organization.

The questionnaire has been translated into Italian from its English version and also from its German version. Subsequently, the translation was checked by an English and German native-speaker professional.

The questionnaire contained scales evaluating the Work Ability Index (WAI and WA-PR), need for recovery, stress levels and general health. The questionnaire data were then matched with physical health data from health surveillance. The questionnaire contained the following elements:

- The Work Ability Index (WAI) by Tuomi et al. [34] includes seven sections: (i) current work ability compared with lifetime best (score range: 1-10); (ii) work ability in relation to mental and physical demands (score range: 2-10); (iii) number of current diseases diagnosed by a physician (score range: 1-7); (iv) estimated work impairment due to diseases (score range: 1-6); (v) sick leave during the past 12 months (score range: 1-5); (vi) self-prognosis of work ability for the next two years (score range: 1-4 or 7); and (vii) mental resources (score range: 1-4). The total score ranges from 7 to 49.
- The Work Ability Personal Radar (WA-PR) [21] conceptualizes the construct of work ability more holistically and subjectively than does the WAI. The WA-PR consists of 17 items that are scored on five different subscales of work ability. Its five subscales are based on the theoretical framework of the work ability house: (i) HF: Health and functional capacity (two items, e.g. "how is your state of health in relation to your work?"; (ii) CO: Competence (three items, e.g. "how is your professional competence?"; (iii) AM: Values, attitudes and motivation (5 items, e.g. "are you appreciated in your workplace?"; (iv) WM: Work organization, work community, and management (four items, e.g. "How well is your work organized"; (v) FS: family life and society (three items, e.g. "How well can you combine your work and your family life?" [21, 31, 32]. Each subscale covers one model element and is measured with two to five items. Items are designed to reflect an individual's subjective experience of these components.
- The last version of the questionnaire contains six additional items investigating the subjective perception of work ability. Considering the model of the house, they represent the roof (Work ability estimate) [8]. The answer options range from 0 to 10 (0 represents the worst evaluation, and 10 represents the best evaluation). These five dimensions constitute the Workplace Wellbeing Index (WPWI) factor. A score below 5 indicates poor workplace well-being, a score between 5-6.99 indicates average workplace well-being, a score between 7-8.99 indicates good workplace

well-being, and a score between 9-10 indicates excellent workplace well-being. The questionnaire also contains six items that refer to the WAI and constitute the work ability estimate index (WAE). Also in this case, the answer options range from 0 to 10 (where 0 is the worst evaluation and 10 is the best evaluation). A total WAE score below 5 indicates a poor work ability estimate, a score between 5-6.99 indicates an average work ability estimate, a score between 7-8.99 indicates a good work ability estimate, and a score between 9-10 indicates an excellent work ability estimate. By summing up all the numerical values of 23 items (WPWI: 17 items; WAE: six questions) and dividing the total by 23, it is possible to obtain the Work Wellbeing Index (WWBI). In recent years, some authors have worked on validating the WA-PR in contexts different from the Finnish one [21], such as in Malaysia [35], Holland and Germany [36].

- The scale of need for recovery [37] contains eight items to identify the need workers have to rest at the end of the working day (e.g. "after a day of work, I feel so tired that I cannot do anything else". The answer options range from 0 to 3 (where 0 is never and 3 is always). The total score ranges from 0 to 24, where 0 indicates a low need for rest while 24 indicates a high need for rest.
- The scale of stress by Copenhagen Psychosocial Questionnaire (COPSOQ) [38] contains seven items to identify the stress level of workers and the behavioral symptoms associated with it (e.g. "I did not have time to relax or have fun". The answer options range from 0 to 3 (where 0 is never and 3 is always). The total score ranges from 0 to 21, where 0 indicates a low-stress level and 21 indicates a high-stress level.
- The scale of general health (created *ad hoc*) contains two items to identify psychological health, both in relation to general and working life, respectively ("How do you rate your psychological well-being in relation to your working life?" "How do you rate your psychological well-being in relation to your general life?". The answer options range from 1 to 10 (where 1 is a negative evaluation and 10 is a positive evaluation). The total score ranges from 2 to 20, where 2 indicates a low level of general health and 20 indicates a high level of general health.
- Concerning the medical records, we considered some indicators of physical health: use of drugs, diagnosis of physical health disorder (of any type), back pain and visual disturbances (the most frequent complaints reported by workers).

2.1. Statistical analysis

About Aim 1, the relationships between variables were tested by correlation. It should be noted that correlations among the WAI, WAE, and WWI include autocorrelations because the WAI contains some items of the WAE, and the WWI integrally contains the WAE and some items of the WAI, thus leading to higher coefficients. We used SPSS (version 26) for our analyses.

Regarding Aim 2, the item analysis included mean, standard deviation, and item-scale correlation. In addition, skewness and kurtosis were used to identify any item deviation from the normal distribution; ideal skewness and kurtosis values are comprised in the range ± 1; however, data was considered normally distributed when skewness $<|3.0|$ and kurtosis $<|7.0|$ [39]. Cronbach's alpha was used to assess internal consistency (values above 0.60 are considered acceptable). A CFA was performed to ascertain the psychometric proprieties of WA-PR and the distinctiveness of subdimensions. In particular, the hypothesized model (six-factors: WAE, FS, WM, AM, CO, and HF) was compared with the one-factor model (the null model), where all items were loaded on the same factor. Model fitting was assessed with the ratio of $\chi 2$ to the degrees of freedom (df), the Comparative Fit Index (CFI), the Standardized Root Mean Square Residual (SRMR) and the Root Mean Square Error of Approximation (RMSEA). According to Kline [39], a $\chi 2$/df ratio of 3 or less indicates a good model fit. For CFI, values higher than 0.90 are considered indicators for good model fit [40]. Values of the SRMR and RMSEA equal to or less than 0.07 indicate a good fit [41, 42].

In addition, the Akaike information criterion (AIC) and the Bayes information criterion (BIC) were used to compare alternative (non-nested) measurement models [39]. The model with the lowest AIC and BIC was considered the best-fitting model. Item factor loading (λ) above 0.40 is considered acceptable [39].

3. Results

The sample comprises 405 respondents (91.8% blue collars and 9.2% white collars). The participants were 62.8% male and 37.2% female, aged 39.8 years and in service for 12.7 years on average (89% with a permanent and 11% with a fixed-term contract). Almost all (98.2%) worked full-time, while only 1.8% of them worked part-time. The factory operates 24 hours per day and 7 days per week: for this reason, 80.5% of the participants worked in shifts.

3.1. Validity

The first aspect analyzed was the relationships between the WPWI, WAE, WWI and WAI. The WPWI correlates substantially in the expected direction, that is, positively, with the WAI (r=0.56); similarly, the WAE correlates with the WAI (always positively: r=0.76). Finally, WWI correlates with the WAI (positively: r=0.64). These correlation effects are moderate and strong, especially for the WAE and WWI. The findings support the assumption that both the WWI and the WPWI, especially the WAE, are closely related to the original WAI. The correlations between the WAE and the WAI, and between WWI and the WAI are partially autocorrelations, thus leading to higher coefficients. In cases of reflective measurement, a corrected item-scale correlation would have to be used, excluding the single item from the scale score before correlating the score with the item. But since each item of the WAI seems to contribute quite special information, not reflecting the variance of a single underlying factor, deleting an item from the WAI could change the measure substantially. To avoid this, we kept the WAI score unchanged [10]. The third aspect is whether the correlational pattern of the WAE, WPWI and WWI with psychological health and stress is similar to that of the WAI. Table 1 shows the correlation coefficients among the WPWI, WAE, WWI and WAI, stress, need for recovery, and general health. As expected, the data show that the WAE, WPWI, WWI and WAI are always correlated in the same direction with the need for recovery, stress, and general health. A stronger relationship is observed between the WAE and general health (r=0.68). Similarly, WWI is strongly correlated with general health (r=0.67), as is WAI (r=0.63).

The fourth aspect is whether the relational pattern of the WAE, WPWI and WWI with physical health is similar to that of WAI (Table 2).

To determine this, we tested the differences among the means of the WAE, WAPWI, WWI and WAI between workers with health diseases (indicators: pharmacological therapy, presence of diseases diagnosed by the doctor during health surveillance,

Table 1. Cross-sectional analyses of the correlation of the WPWI, WAE, WWI and WAI with the need for recovery, stress, and general health.

	WPWI	WWI	WAI	Need for recovery	Stress	General health
WAE	.729**	.845**	.760**	-.549**	-.452**	.678**
WPWI	-	.982**	.559**	-.409**	-.437**	.622**
WWI		-	.642**	-.477**	-.481**	.669**
WAI			-	-.578**	-.505**	.628**
Need for recovery				-	.691**	-.457**
Stress					-	-.526**

** $p<0.01$

Table 2. Analyses of tests of the WPWI, WAE, WWI and WAI with the physical dimensions (pharmacological therapy, presence of diseases diagnosed by the doctor during health surveillance, back pain and visual diseases).

	Pharmacological therapy	**N**	**M**	**SD**	**T**	***P***
WAI	No	190	38.97	5.58	5.53	.000
	Yes	77	33.86	7.29		
WAE	No	244	7.59	1.34	5.02	.000
	Yes	116	6.62	1.86		
WPWI	No	214	7.15	1.47	2.22	.027
	Yes	91	6.74	1.59		
WWI	No	205	7.28	1.36	3.17	.002
	Yes	89	6.70	1.55		
	Physical diseases	**N**	**M**	**SD**	**T**	***P***
WAI	No	146	39.32	5.84	5.15	.000
	Yes	122	35.38	6.71		
WAE	No	175	7.77	1.32	5.90	.000
	Yes	186	6.83	1.69		
WPWI	No	154	7.44	1.39	4.99	.000
	Yes	152	6.61	1.52		
WWI	No	148	7.56	1.29	5.68	.000
	Yes	147	6.65	1.45		
	Back pain	**N**	**M**	**SD**	**T**	***P***
WAI	No	144	39.92	5.59	6.99	.000
	Yes	137	34.80	6.63		
WAE	No	181	7.71	1.35	5.21	.000
	Yes	199	6.89	1.72		
WPWI	No	165	7.33	1.48	3.99	.000
	Yes	158	6.65	1.59		
WWI	No	159	7.46	1.36	4.59	.000
	Yes	152	6.71	1.52		
	Visual diseases	**N**	**M**	**SD**	**T**	***P***
WAI	No	203	38.10	6.33	2.73	.007
	Yes	78	35.70	7.09		
WAE	No	265	7.47	1.47	3.28	.001
	Yes	115	6.84	1.81		
WPWI	No	233	7.07	1.58	1.31	NS
	Yes	90	6.82	1.54		
WWI	No	224	7.19	1.46	1.94	NS
	Yes	87	6.83	1.52		

back pain, and visual diseases) and without health diseases (no pharmacological therapy, absence of diseases diagnosed by the doctor during health surveillance, no back pain and no visual diseases).

Regarding visual diseases, the data showed statistical differences between workers who have visual diseases and workers who do not have visual diseases for the WAI and WAE but not for the WPWI or WWI. These data confirm that the three dimensions of the WA-PR are very similar to the WAI and, precisely like the WAI, are related to physical health indicators, especially pharmacological therapy, physical diseases, and back pain.

Regarding pharmacological therapy, the data showed statistical differences between workers who consume pharmaceutical drugs and workers who do not consume drugs for all work ability indicators considered (WAI, WAE, WPWI, WWI). The t-test is very similar between the WAI and WAE.

Regarding the presence of diseases diagnosed by the doctor during health surveillance, the data showed statistical differences between workers who have diseases and workers who do not have diseases for all work ability indicators considered (WAI, WAE, WPWI, WWI). The t-test is very similar across all work ability indicators.

Concerning the presence of back pain, the data showed statistical differences between workers who have diseases and workers who do not have diseases for all work ability indicators considered (WAI, WAE, WPWI, WWI). The t-test is very similar across all work ability indicators.

3.2. Psychometric properties

3.2.1 Item analysis and internal consistency

Descriptive statistics for the items are shown in Table 3. For all items, the corrected item-total correlation achieved values equal to or greater than r=0.50; the only exception was Item 3 ("How is your professional competence?" belonging to the CO scale, with a corrected item-total correlation of 0.26.

Regarding skewness, Items 1, 2, 3, 7, 8, 10, 12, 14, 20, 21 and 22 were slightly out of the range of -1 and +1; however, all values were between the range of -3 and +3. Similarly, regarding kurtosis, Items 1, 2, 3, 4, 7, 12, 14, 18, 19, 20 and 21 were out of the range of |1| but within the range of |7|.

Regarding internal consistency, all the subdimensions reported acceptable values of Cronbach's alpha, except for CO, which showed a value of 0.56. The computation of alpha after deleting an item indicated that without Item 3, the alpha of the CO scale would see a substantial improvement, reaching a value of 0.62.

3.2.2 Confirmatory factor analysis

Table 4 reports the global fit index of the CFA carried out. Considering the deviations (though not severe) from the normal distribution of some items of the WA-PR, to minimize the risk of finding distortions, Maximum Likelihood Robust (MLR), which is robust to non-normality, was employed as an estimation method.

The hypothesized six-factor model, which considered all the WA-PR subdimensions as distinct factors, fit the data significantly better than the one-factor model. However, the fit of this six-factor model has not been completely satisfactory since the CFI value was below 0.90. In this solution, all items significantly loaded on their corresponding factor and reported factor loadings (λ) higher than 0.60 (Table 5). The only exception was Item 3, which reported a factor loading of 0.37, which was significant, but below 0.40.

Since both CroCronbach'spha and CFA suggested that Item 3 might compromise the functioning of the scale to which it belongs (CO), an alternative version of the six-factor model was carried out without including Item 3. This model showed an acceptable fit to the data ($\chi2$=539.74, df=194, $\chi2$/df=2.78, CFI=0.91, SRMR=0.06, RMSEA=0.07[0.06-0.07]), and each item significantly loaded on its corresponding factor, with a saturation higher than 0.60. All subdimensions significantly and positively correlated with each other, showing an r-value higher than 0.40.

4. Discussion

Our data show that WPWI, WAE and WWI correlated clearly with the WAI and that the three dimensions of the WA-PR correlated in the

Table 3. Item analyses and Cronbach's alphas.

Subscale Item	*M* (SD)	Corrected item-scale Correlations	Skewness	Kurtosis	Alpha if item deleted
HF (α=.66)					
1	7.27(2.08)	.51	-1.13	1.71	--
2	8.00(1.58)	.51	-1.29	3.40	--
CO (α=.56)					
3	7.95(1.46)	.26	-1.34	4.20	.62
4	7.34 (1.97)	.55	-.98	1.53	.21
5	6.43 (2.87)	.41	-.80	-.25	.49
AM (α=.92)					
6	6.32 (2.68)	.78	-.82	-.02	.89
7	7.50(2.17)	.71	-1.25	1.85	.91
8	7.00 (2.29)	.85	-1.01	.90	.88
9	6.60 (2.61)	.88	-.84	.06	.87
10	6.72 (2.53)	.72	-.96	.49	.91
WM (α=.82)					
11	6.63(2.14)	.68	-.91	.84	.76
12	7.29 (2.38)	.71	1.18	1.25	.74
13	6.25 (2.57)	.67	-.76	.12	.76
14	7.30 (2.14)	.52	. -1.19	1.59	.83
FS (α=.84)					
15	6.61 (2.59)	.65	-.92	.36	.84
16	6.90 (2.18)	.80	-.82	.53	.69
17	6.63 (2.26)	.68	-.61	.00	.80
WA (α=.87)					
18	6.88 (1.92)	.58	-.85	1.23	.85
19	8.09 (1.44)	.58	-.95	2.26	.86
20	7.71 (1.88)	.75	-1.12	1.79	.83
21	7.57 (1.80)	.74	-1.07	1.77	.83
22	7.59 (2.17)	.76	-1.03	.96	.82
23	5.79 (2.81)	.64	-.57	-.56	.86

Table 4. Confirmatory factor analyses (CFA): test of alternative models (good-of-fit indices).

	χ^2	df	χ^2/df	CFI	SRMR	RMSEA [CI]	AIC	BIC
M0. One-factor model	1352.27	230	5.87	.71	.10	.11[.10-.11]	36389.94	36666.21
M1. Six-factor model	627.32	215	2.92	.89	.07	.07[.06-.07]	35247.30	35583.63
M1a. Six-factor model (no item 3)	539.74	194	2.78	.91	.06	.07[.06-.07]	33831.54	34155.86

Note: df=degree of freedom. CFI=comparative fit index. SRMR=sstandardizedroot mean square residual. RMSEA=root mean square error of approximation. AIC=Akaike information criterion. BIC=Bayes information criterion.

Table 5. Confirmatory factor analyses (CFA): factor loadings and standard errors.

Model	**MO**		**M1**		**M1.a**	
	λ	standard error	λ	standard error	λ	standard error
HF						
1	.67	.04	.83	.04	.83	.04
2	.53	.05	.62	.06	.62	.06
CO						
3	.35	.06	.33	.06	--	--
4	.68	.03	.65	.04	.65	.04
5	.75	.02	.73	.03	.73	.04
AM						
6	.77	.03	.82	.03	.82	.03
7	.75	.03	.76	.03	.76	.03
8	.83	.02	.90	.01	.90	.01
9	.87	.02	.92	.01	.92	.01
10	.71	.04	.76	.03	.76	.03
WM						
11	.80	.02	.82	.03	.81	.03
12	.72	.04	.78	.04	.78	.04
13	.69	.03	.75	.03	.76	.03
14	.57	.05	.59	.05	.59	.05
FS						
15	.58	.05	.76	.03	.76	.03
16	.53	.05	.89	.03	.89	.03
17	.50	.05	.79	.03	.79	.03
WA						
18	.71	.04	.66	.04	.66	.04
19	.48	.06	.63	.04	.63	.04
20	.59	.05	.82	.03	.82	.03
21	.65	.04	.79	.03	.79	.03
22	.66	.04	.82	.02	.82	.02
23	.64	.04	.71	.03	.71	.03

expected directions with constructs conceptually related to work ability, both psychological and physical (specifically: need for recovery, stress, and general health).

More specifically, the WPWI, WAE and WWI correlated with the WAI, demonstrating a construct that is almost stackable to the work ability measured by the WAI. In another way, the WPWI, WAE and WWI, exactly like the WAI, correlated negatively with stress and need for recovery and positively with general health. All the WA measures show very similar correlations with need for recovery, stress, and general health. These data confirm two aspects: first, the three dimensions of the WA-PR are very similar to those of the WAI and, exactly like the WAI, correlated with outcomes of psychological health (in this case, need for recovery, stress, and general health); the second aspect is that the three dimensions of the WA-PR correlated negatively with need for recovery and stress and positively with general health.

Similarly, the WPWI, WAE and WWI, exactly like the WAI, are related with physical diseases. In this direction, low levels of WPWI, WAE, WWI and WAI are related to the presence of pathologies diagnosed by the medical doctor, the use of drug therapy, the presence of back pain and visual disturbances. That the WAI correlates with physical health is not surprising, because it contains at least one item (Item 3) that included medical dimensions, constructs that overlap.

However, it is interesting that even more subjective evaluations of work ability (WPWI, WAE, WWI) are related to the dimensions of physical health.

Generally, our findings confirm that the WA-PR is a useful and reliable tool for evaluating work ability and better reflects the WA home model. In this direction, the tool is useful for individualizing the subjective dimension of the WA and the antecedents that can influence it. In conclusion, the WA-PR is a good tool for assessing work ability in a more holistic view of the same. In this direction it overcomes the limits of the WAI, centered mainly on physical dimensions and diseases and less on the perceived experience of workers, moreover WAI excludes psycho-social aspects of work that are important in the definition of WA.

However, some considerations should be made regarding Item 3. Both Cronbach's alpha and CFA suggested that it compromised the functioning of the CO scale. A possible explanation for this finding would be that Item 3 refers to a distinct content domain when compared with the rest of the items of the scale. While with Item 3, the respondents are asked to assess their own competence, while the other two assess the capability of the job and the organizational context to offer to the worker growth and development opportunities. In other words, it is plausible that the underlying criteria to which respondents refer to give answers to Item 3 on one hand and Items 4 and 5 on the other hand would have been different. Future studies should further verify the results we obtained here regarding Item 3, both in similar (i.e. manufacturing industries) and different occupational contexts (e.g. healthcare or teaching sectors). Future studies should also include additional items both regarding the domain of self-assessment competence and the domain of the opportunity for development in the workplace to better understand whether these aspects can be explained by only one dimension or whether two distinct dimensions are needed.

4.1. Limitations of the study

A first limitation of the study concerns the average age of the people interviewed: the mean age of study sample is under 40 (39.8, which is younger that the mean age of Italian workers). The young age of our study subjects is a limitation because the literature shows that WA is strongly associated with age.

A second limitation could be given by the specificity of the workers and the context considered (shift worker in the chemical sector). This could be considered potential limitation in the generalization of the results.

Institutional review board statement: The study was conducted according to the guidelines of the Declaration of Helsinki.

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Declaration of interest: The authors declare no conflict of interest.

References

1. Ilmarinen J, Tuomi K, Eskelinen L, Nygard CH, Huuhanen P, Klockars M. Background and objective of the Finnish research project on aging workers in municipal occupation. *Scand J Public Health*. 1991;17:7-11.
2. Bakker AB, Demerouti E. The job demands resources model: state of art. *J Manag Psychol*. 2007;22: 309-328.
3. Brady GM, Cadiz DM, Truxillo DM, Rineer JR. Opening the Black Box: Examining the nomological network of work ability and its role in organizational research. *J Appl Psychol*. 2020;105(6):637-670. Doi:101037/apl0000454

4. Tuomi K, Vanhala S, Nykyri E, Janhonen M. Organizational practices, work demands and well-being of employees: a follow up study in the mental industry and retail trade. *Occup Med*. 2004;54:115-121. Doi: 10.1093/occmed/kqh005
5. Feldt T, Hyvonen K, Makikangas A, et al. Development trajectories of Finnish managers' workabilityer 10-years follow up period. *Scand J Work Environ Health*. 2009;35:37-47. Doi: 10.5271/sjweh.1301
6. Hatch DJ, Freude G, Martus P, et al. Age, burnout and physical and psychological work ability among nurses. *Occup Med*. 2018;68(4):246-254. Doi: 10.1093/occmed/kqy033
7. Converso D, Sottimano I, Balducci C. Violence exposure and burnout in heathcare sector: mediating role of work ability. *Med Lav*. 2021;112(1):58-67. Doi: 10.23749/mdl.v112i1.9906
8. Ilmarinen J. From Work Ability Research to Implementation. *Int J Environ Res Public Health*. 2019;16(16):2882. Doi:10.3390/ijerph16162882
9. Tuomi K, Ilmarinen J, Seitsamo J, et al. Summary of the Finnish research project (1981-1992) to promote the health and work ability of aging workers. *Scand J Work Environ Health*. 1997;23:66-71.
10. Ebner M, Hasselhorn HM. Validation of Short Measures of work ability for research and employee surveys. *Int J Environ Res Public Health*. 2019;16:3386. Doi: 10.3390/ijerph16183386
11. Hasselhorn HM, Freude G. Der Work ability index. Ein Leitfaden. Bremerhaven, Germany, 2007.
12. Martus P, Jakob O, Rose U, et al. Comparative analysis of the Work Ability Index. *Occup Med*. 2010;60:517-524.
13. Radkiewicz P, Widerszal-Bazyl M. Psychometric properties of Work Ability Index in the light of comparative survey study. *Int. Congr. Ser*. 2005;1280:304-309.
14. Martinez MC, Do Rosário Dias de Oliveira Latorre M, Fischer FM. Validity and reliability of the Brazilian version of the Work Ability Index questionnaire. *Rev Saude Publica*. 2009;43:525-532.
15. Abdolalizadeh M, Arastoo AA, Ghsemzadeh R, et al. The psychometric properties of an Iranian translation of the Work Ability Index (WAI) questionnaire. *J Occup Rehabil*. 2012;22:401-408.
16. Peralta N, Godoi Vasconcelos AG, Härter Griep R, Miller L. Validez y confiabilidad del Índice de Capacidad para el Trabajo en trabajadores del primer nivel de atención de salud en Argentina. *Salud Colect*. 2012;8:163-173.
17. Kaewboonchoo O, Ratanasiripong P. Psychometric properties of the Thai version of the work ability index (Thai WAI). *J Occup Health*. 2015;57:371-377.
18. Freyer M, Formazin M, Rose U. Factorial Validity of the Work Ability Index Among Employees in Germany. *J Occup Rehabil*. 2018;29:433-442.
19. Freyer M, Formazin M, Rose U. Work Ability Index: Eine neue Berechnungsmethode auf Basis von zwei-Faktoren. Arbmed. Sozmed. *Umweltmed*. 2019;54.
20. Morschauser M, Sochert R. Healthy work in an ageing Europe. Essen Germany: Federal Association of Company Health Insurrance Funds. 2006. pp. 1-76.
21. Ilmarinen V, Ilmarinen J, Huuhtanen P, et al. Examining the factorial structure, measurement invariance and convergent and discriminate validity of a novel self-report measure of work ability: work ability – personal radar. *Ergonomics*. 2015;58(8):1445-60. Doi: 10.1080/00140139.2015.1005167
22. Ahlstrom L, Grimby-Ekman A, Hagberg M, Dellve L. The work ability index and single-item question: Associations with sick leave, symptoms, and health A prospective study of women on long-term sick leave. *Scand J Work Environ Health*. 2010;36:404-412.
23. Donaldson SI, Grant-Vallone EJ. Understanding self-report bias in organizational behavior research. *J Bus Psychol*. 2002;17:245-260.
24. Alavinia SM, De Boer AGEM, Van Duivenbooden JC, et al. Determinants of work ability and its predictive value for disability. *Occup Med*. 2009;59:32-37.
25. Weigl M, Müller A, Hornung S, et al. The moderating effects of job control and selection, optimization and compensation strategies on the age-work ability relationship. *J Organiz Behav*. 2013;34:607-628.
26. Vingård E, Lindberg P, Josephson M, et al. Long-term sick-listing among women in the public sector and its associations with age, social situation, lifestyle, and work factors: A three-year follow-up study. *Scand J Public Health*. 2016;33:370-375.
27. Cadiz DM, Brady G, Rineer JR, et al. A Review and Synthesis of the Work Ability Literature. *Work Aging Retire*. 2018;5:114-138.
28. Palermo J, Fuller-Tyszkiewicz M, Walker A, Appannah A. Primary and secondary level organizational predictors of work ability. *J Occup Health Psych*. 2013;18(2):220-229.
29. McGonagle A, Fisher GG, Barness-Farrell JL, Grosch JW. Individual and work factors related to perceived work ability and labor force outcomes. *J Appl Psychology*. 2015;100(2):376-398.
30. Hetzel C, Baumann R, Bilhuber H, Mozdzanowski M. Determination of work ability by a Work Ability Index short form ("WAI-r"). *ASU International*. 2014(10);01-03.
31. Ilmarinen J, Tuomi K, Seitsamo J. New Dimensions of Work Ability. *International Congress Series*. 2005;1280:3-7. Doi:10.1016/j.ics.2005.02.060
32. Gould R, Ilmarinen J, Järvisalo j, Koskinen S. Dimensions of Work Ability – Results of the Health 2000 Survey. Helsinki: Finnish Centre for Pensions, The Social Insurance Institution, National Public Health Institute, Finnish Institute of Occupational Health. Eds. 2008.
33. Demerouti E, Bakker AB, Nachreiner F, Schaufeli WB. The job demands-resources model of burnout. *J Appl Psychol*. 2001;86(3):499-512.

34. Tuomi K, Ilmarinen J, Jahkola A, et al. Work Ability Index. 2nd revised ed.; Helsinki: Finnish Institute of Occupational Health, 1998.
35. Abas Hamdan A, Puteh F, Abu A. Measuring the validity and reliability of the work ability personal radar questionnaire using Malay language version. Qualitative and Quantitative Research Review. 2019;4(3).
36. BAUA.https://www.baua.de/DE/Angebote/Veranstaltungen/Dokumentationen/Demografie/pdf/Demografie-Wissen-kompakt-2016-10.pdf?_blob=publicationFile&v=2
37. Pace F, Lo Cascio V, Civilleri A, et al. The need for recovery scale: adaptation to Italian Context. *Eur Rev Appl Psychol*. 2013;63:243-249.
38. Pejtersen JH, Kristensen TS, Borg V, Bjorner JB. The second version of the Copenhagen Psychosocial Questionnaire. *Scand J Public Health*. 2010;38:8. Doi: 10.1177/1403494809349858
39. Kline RB. Principles and Practice of Structural Equation Modeling, 2nd ed. Guilford, New York. 2011
40. Bentler PM. EQS structural equations program manual. 1995.
41. Byrne BM. Structural equation modeling with LISREL, PRELIS and SIMPLIS: Basic concepts, applications and programming. Mahwah, NJ: Erlbaum. 1998
42. Hu L, Bentler PM. Cut-off criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling*. 1999;6:1-55. Doi:10.1080/10705519909540118

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Identification of a new potential plasmatic biomarker panel for the diagnosis of malignant pleural mesothelioma

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Keywords: Malignant pleural mesothelioma; respiratory disease; asbestos exposure; circulating biomarkers

Abstract

Background: *Malignant pleural mesothelioma (MPM) is a rare, highly aggressive tumor strongly associated with asbestos exposure and characterized by poor prognosis. Currently, diagnosis is based on invasive techniques; thus, there is a need to identify non-invasive biomarkers to detect the disease. In the present study, we measured the plasmatic concentrations of Mesothelin, Fibulin-3, and HMGB1 protein biomarkers and of hsa-miR-30e-3p and hsa-miR-103a-3p Extracellular-Vesicles- embedded micro RNAs (EV-miRNAs). We tested the ability of these biomarkers to discriminate between MPM and PAE subjects alone and in combination.* **Methods:** *The study was conducted on a population of 26 patients with MPM and 54 healthy subjects with previous asbestos exposure (PAE). Mesothelin, Fibulin-3, and HMGB1 protein biomarkers were measured by the enzyme-linked immunosorbent assay (ELISA) technique; the levels of hsa-miR-30e-3p and hsa-miR-103a-3p EV-miRNAs was assessed by real-time quantitative PCR (qPCR).* **Results:** *The most discriminating single biomarker resulted to be Fibulin-3 (AUC 0.94 CI 95% 0.88-1.0; Sensitivity 88%; Specificity 87%). After investigating the possible combinations, the best performance was obtained by the three protein biomarkers Mesothelin, Fibulin-3, and HMGB1 (AUC 0.99 CI 95% 0.97-1.0; Sensitivity 96%; Specificity 93%).* **Conclusions:** *The results obtained contribute to identifying new potential non-invasive biomarkers for diagnosing MPM. Further studies are needed to validate the evidence obtained to assess the reliability of the proposed biomarker panel.*

1. Introduction

Malignant pleural mesothelioma (MPM) is an aggressive and highly lethal cancer originating from the pleura's mesothelial cells after asbestos exposure [1, 2]. Although MPM is considered a rare malignancy with an incidence of 1:100,000, about 40,000 deaths worldwide have been estimated to occur each year globally for asbestos exposures, with a long latency of between 30 and 50 years [3-5].

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MPM diagnosis is still conducted by thoracoscopic biopsy, an invasive and costly approach [6, 7]. The dismal prognosis of MPM is attributable to different factors, such as late diagnosis mainly due to typically subtle and nonspecific clinical symptoms, unpredictable tumor growth, and minimal response to current treatment protocols, the average survival time being 13 months [8-10].

In this scenario, the identification of reliable non-invasive biomarkers of disease to be used in high-risk populations is challenging [11, 12]. Several strategies have been explored to develop robust minimal invasive tests starting from liquid biopsies [11, 13]. Circulating biomarkers are found in different body fluids, such as serum, plasma, and pleural effusions, with the potential to diagnose MPM early, even before clinical imaging techniques [11, 13, 14]. Various studies have investigated different types of potential circulating biomarkers. Mesothelin, Fibulin-3, and High Mobility Group B1 protein (HMGB1) are the most promising ones to be further validated and tested in combination in independent populations [15]. Circulating nucleic acids, such as DNA, RNA, and microRNAs (miRNAs), have also been examined as potential MPM biomarkers [16]. In particular, miRNAs embedded within circulating extracellular vesicles (EV-miRNA) might be particularly interesting. Indeed, E.V.s are membrane-bound structures that contain several bioactive molecules, such as miRNA, and are released by cells to promote intercellular communication [17, 18]. Thus, it is plausible that specific EV-miRNA signatures may represent the active crosstalk between MPM cells and immune cells rather than a passive result of miRNA accumulating in plasma as a waste product [19].

In a previous study, we measured the expression of 754 circulating EV-miRNAs in 23 patients with MPM and 19 cancer-free subjects with past asbestos exposure (PAE). We identified the two EV-miRNA signatures, i.e., hsa-miR-30e-3p and hsa-miR-103a-3p, as the best discriminating combination between MPM and PAE groups [20]. In the present study, we evaluated, in a larger population, the plasmatic expression of the EV-miRNA signature previously identified and that of the circulating Mesothelin, Fibulin-3, and HMGB1 protein biomarkers. Moreover, we tested the discriminating potential of different combinations of the examined biomarkers and presented evidence that the combination of Mesothelin, Fibulin-3, and HMGB1 showed the best discrimination performance.

2. Methods

2.1 Study population

The study population includes patients with MPM and subjects with past occupational asbestos exposure. The MPM patients were enrolled at the Thoracic Surgery Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, between October 2013 and August 2016. MPM diagnosis was performed on pleural biopsies collected during video-assisted thoracoscopy surgery. Tissue specimens were classified according to the TNM staging system established by the International Mesothelioma Interest Group (IMIG) and the International Association for the Study of Lung Cancer (IASLC) [21-23]. The 54 PAE subjects underwent a clinical surveillance program in the same study period as MPM subjects at the Occupational Health Unit Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, as established by the Italian Law Dlgs 81/2008.

2.2. Asbestos exposure assessment

As previously described, information on detailed asbestos exposure in both occupational and environmental settings was collected through a standardized questionnaire administered to each subject by trained interviewers [20, 24]. Demographic, lifestyle, and smoking information was also collected in that context.

2.3. Blood collection, plasma separation, E.V. isolation, and EV-miRNA extraction

Each study participant was asked to donate a 7.5 ml blood sample, collected in 3K-EDTA Vacutainer plastic tubes (Becton Dickinson, New Jersey, USA) and processed within 3 h of the blood draw. None of the MPM patients underwent surgery, chemo- or radiotherapy before blood collection. Blood was centrifuged at 400 g for 15 min to separate the plasma fraction from the blood cells. For EV-miRNA analysis, plasma samples were centrifuged three times at 1000 g, 2000 g, and 3000 g for 15 min at 4 °C to remove cell debris and aggregates. Supernatants were ultracentrifuged at 110000 g for 2 h at 4 °C. EV-miRNAs were isolated as previously described [20]. Briefly, miRNAs were isolated with the miRNeasy purification kit (Qiagen Hilden, Germany) following the manufacturer's instructions and eluted in 25 μl of elution buffer. miRNA quality after purification was analyzed with the 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA) using Agilent RNA 6000 Pico Kit. Isolated miRNAs were concentrated with Concentrator Plus (Eppendorf, Hamburg, GER) to 6.7 μl and stored at -80 °C until use.

2.4. Protein analysis

Plasmatic mesothelin was measured using the enzyme-linked immunosorbent assay (ELISA) kit MESOMARK (Fujirebio Diagnostics, Inc., Malvern, PA, USA) as described previously [25]. ELISA for Fibulin-3 coding protein was conducted according to the manufacturer's instructions using the Human EFEMP1 PicoKine ELISA Kit (Boster Bio, Pleasanton, CA, USA) [26]. The HMGB1 protein levels were assessed by the kit HMGB1 express ELISA (IBL International GmbH, Hamburg, Germany), as reported by Handke N.A. and colleagues [27]. Absorbance was measured at 450 nm using the microplate reader Sinergy HT (Santa Clara, CA, USA). All samples were tested in duplicate.

2.5. EV-miRNA analysis

Expression quantification of hsa-miR-30e-3p and hsa-miR-103a-3p EV-miRNAs was determined by Custom TaqMan™ microRNA assay (Thermo Fisher Scientific, Waltham MA, USA) following standard procedures. Briefly, each miRNA was analyzed in triplicate, and RNU48 was used for data normalization. Specific reverse transcription of miRNAs was performed following standard procedures. R.T. was performed using a C1000 Thermal Cycler (Bio-Rad, Hercules, CA, USA), and the cDNAs were pre-amplified. After the pre-amplification product was diluted at 1:8, quantitative RT-PCR was run in a Quant Studio 12K Flex Fast Real-Time PCR System (Thermo Fisher Scientific), according to the manufacturer's protocol. miRNA expression was calculated by the comparative cycle threshold (ΔCT) method and analyzed with SDS software (Thermo Fisher Scientific).

2.6. Statistical analysis

Data were expressed as mean and standard deviation when normally distributed, otherwise by the median, with the minimum, maximum, and first and third quartiles. Frequencies and percentages were calculated for categorical variables. The differences between the MPM patients and PAE subjects' groups were compared using Pearson's chi-square test, Fisher's Exact test for categorical data, or t-test or Mann-Whitney U-test for continuous variables, as appropriate. Spearman correlation coefficients were obtained from each pair of plasmatic biomarkers. To evaluate the levels of biomarkers for the TNM stages, histotype, and survival, we applied ANOVA models after the log transformation of biomarkers. We reported the geometric means of biomarker and the p-values of comparisons between each TNM stage and stage I, set as the reference category, and the overall p-value of the differences across the four stages.

Univariate logistic regression was performed to investigate the association between potential MPM-associated risk factors (i.e., gender, age, body mass index (BMI), and smoking habits) on the risk of MPM. Multivariate logistic regression, adjusted for gender, age, BMI, and smoking habits, was performed to investigate the association between each plasmatic biomarker and the risk of MPM. The estimated effects were reported as odds ratios (OR) and 95% Confidence Intervals (CI) associated with a unit increase of each biomarker.

Receiver-Operating Characteristic (ROC) curves were generated to evaluate the diagnostic ability of each biomarker to distinguish between subjects with MPM and PAE subjects, and the area under the ROC curve was computed to assess their discriminant performance. Sensitivity, specificity, true positive (T.P.), and true negative (T.N.) values for MPM were calculated for each biomarker of interest and their combination.

We thus investigated the discrimination ability of the combination of Mesothelin, Fibulin-3, and HMGB-1, comparing to that generated by each of them taken alone, or in combination, irrespectively to the abovementioned covariates. Statistical significance was defined as $p<0.05$. Statistical analyses were performed with SAS software, version 9.4, and R software, version 3.6.3.

3. Results

3.1. Characterization of the study participants

The study participants include 26 patients with MPM and 54 subjects with past asbestos exposure, whose main characteristics are reported in Table 1. Most subjects in each group were males (77% MPM; 87% PAE). The mean age was 71.3 (±7.8) years for patients with MPM and 64.8 (±6.0) for PAE subjects. Smoking habits and the categorical distributions of BMI means did not differ ($p=0.417$; $p=0.084$) between the two groups. Asbestos exposure was established in 57.7% of MPM cases, most of which (n=14) had occupational exposure. Duration of exposure and time since last exposure were higher in patients with MPM than in PAE subjects ($p=0.036$ and 0.006, respectively) and patients with MPM showed a longer latency (years since first exposure to the diagnosis of MPM or blood collection for PAE subjects; $p=0.006$). The most frequent histological MPM types were epithelioid (n=14) and biphasic (n=10). 81% of MPM was T1-T2, and 21 cases (19 in the T1-T2 size category; 2 in T4) had no metastases at diagnosis. The TNM was also determined and reported in Table 1.

3.2 Expression profiles of plasmatic biomarkers

Expression profiles of the plasmatic levels of Mesothelin, Fibulin-3, and HMGB1 proteins, EV-miRNA hsa-miR-103a-3p, and hsa-miR-30e-3p are reported in Table 2. All the protein biomarkers showed higher expression in MPM patients than in PAE controls. On the contrary, both hsa-miR-103a-3p and miR-30e-3p expression was lower in MPM cases (fold change 0.57 and 0.76, respectively). In particular, the greatest difference between MPM and PAE was observed for Mesothelin and hsa-miR-103a-3p.

Moreover, we investigated the possible correlations of the tested biomarkers with the TNM subgroups and histotype. As reported in Supplementary Tables S1 and S2, no differences were found. We further tested the correlation between the different biomarkers and observed that the two EV-miRNAs hsa-miR-30e-3p and hsa-miR-103a-3p were the most correlated ($r=0.97$), followed by Fibulin-3 and HMGB1 ($r=0.41$), as reported in Figure 1.

3.3. Discrimination between patients with MPM and PAE subjects

By logistic regression, we estimated the odds of being a patient with MPM for each measured biomarker and the covariates considered in the analyses (i.e., gender, BMI, and smoking habits) (supplementary tables S3 and S4). Moreover, to examine the discrimination ability between patients with MPM and PAE subjects, we fitted multiple logistic regression models adjusted for gender, age, BMI, and smoking habits and calculated adjusted receiver operating characteristic (ROC) curves for each one of the biomarkers taken into consideration (Table 3; Figure 2). The best discriminating biomarkers were Fibulin-3, HMGB-1, and Mesothelin, and the areas under the curve (AUC) were, respectively, 0.94, 0.92, and 0.88. Thus, we investigated the discrimination ability of the different combinations of these three biomarkers. The use of all three proteins generated an AUC of 0.99, with a Sensitivity of 96% and a Specificity of 93%, slightly higher than the combination of Mesothelin and Fibulin-3 only (AUC=0.98, Sensitivity 92%, specificity 91%). In addition, the estimate of ROC difference between the combination only of Fibulin-3 and Mesothelin, with that of the three biomarkers HMGB-1, Fibulin-3 and Mesothelin did not reach significance ($p= 0.674$; Supplementary Table S5).

Table 1. Characteristics of MPM and PAE subjects.

	MPM n=26	PAE n=54	p-value
Gender			0.333§
Male	20 (77%)	47 (87%)	
Female	6 (23%)	7 (13%)	
Age, years, (mean±SD)	71.3±7.8	64.8±6.0	<0.001^{w}
Smoking habits			0.417^{c}
Non-smokers	8 (31%)	25 (46%)	
Former smokers	15 (58%)	24 (44%)	
Smokers	3 (12%)	5 (9%)	
Categorical BMI			0.084^{c}
Underweight (BMI < 18.5)	16 (62%)	19 (35%)	
Lean (18.5 ≤ BMI < 25)	7 (27%)	24 (44%)	
Overweight (BMI > 25)	3 (12%)	11 (20%)	
Asbestos exposure categorization			
Occupational	14 (53.8%)	54 (100%)	
Environmental	1 (3.8%)	0 (0%)	
Unknown	11 (42.3%)	0 (0%)	
Duration of exposure, years, median (min, Q1, Q3, max)	25 (1, 17, 32, 47)	11 (0, 6, 25, 40)	0.036*
Latency years, median (min, Q1, Q3, max)	55 (24, 47, 60, 67)	44 (12, 37, 49, 59)	0.006*
Histology			
Epithelioid	14 (54%)		
Biphasic	10 (38%)		
Sarcomatoid	2 (8%)		
Tumor size			
T1-T2	21 (81%)		
T3	0 (0%)		
T4	5 (19%)		
Lymph Node Status			
N0	10 (38%)		
N1	8 (31%)		
N2	8 (31%)		
Metastases at diagnosis			
No	21 (81%)		
Yes	5 (19%)		
TNM staging			
I	8 (31%)		
II	6 (23%)		
III	7 (27%)		
IV	5 (19%)		

S.D., standard deviation; min, minimum, max, maximum, Q1, Q3, first-third quartile; ^{c}*p-value from Pearson's chi-square test.* ^{w}*p-value from t-test.* $^{\$}$*p-value from Fisher's Exact test. *p-value from Mann-Whitney U-test. Tissue specimens were classified according to the TNM staging system established by IMIG and IASLC.*

Table 2. Description of protein and EV-miRNA in MPM and PAE subjects.

Biomarker	Mean±standard deviation MPM n=26	PAE n=54	p-value
Mesothelin, ng/ml	3.8±5.8	0.9±0.5	0.015[w]
Fibulin-3, ng/ml	53.9±18	44.6±2.9	0.014[w]
HMGB1, ng/ml	12±11.2	5.4±5.2	0.008[w]
hsa-miR-103a-3p	568.2±408.7	1001.4±364.2	0.001*
hsa-miR-30e-3p	368.7±264	484.7±171.5	0.021*

[w]*p-value from t-test.*
**p-value from Mann-Whitney U-test.*

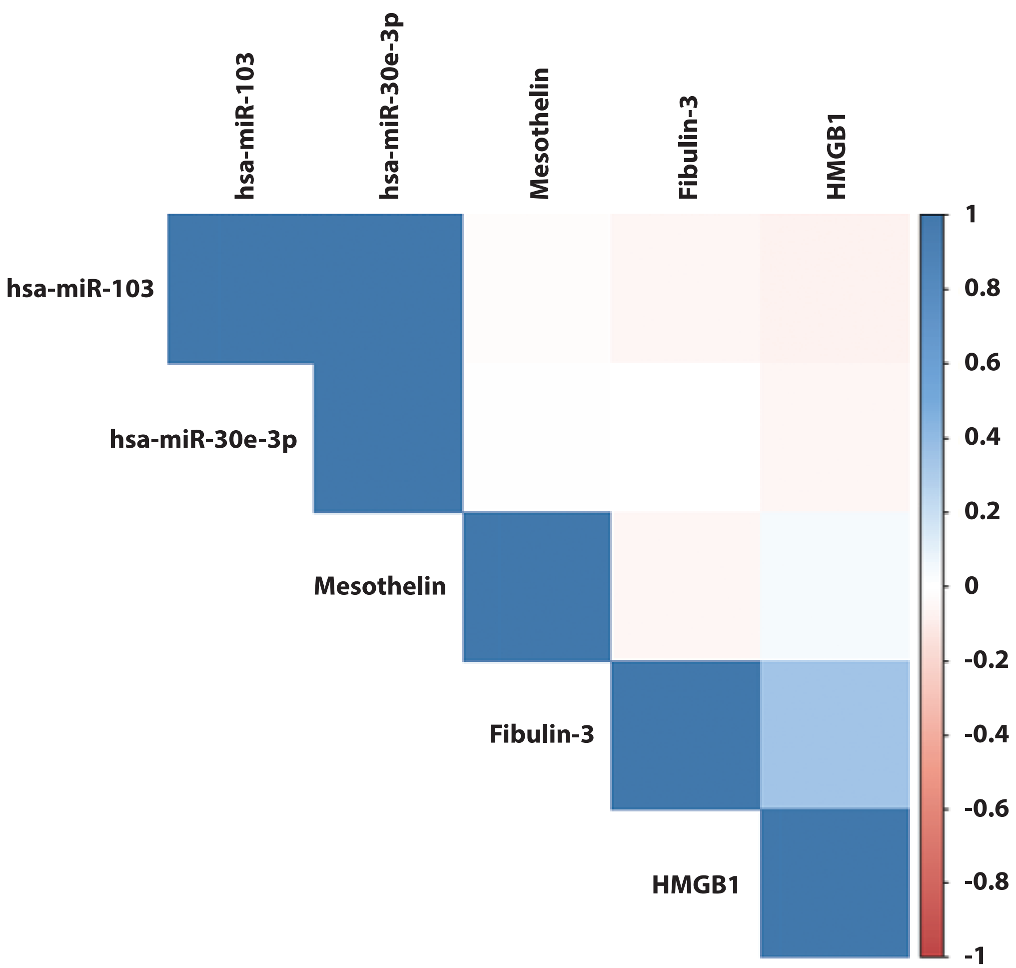

Figure 1. Correlation plot of plasmatic biomarkers (proteins and EV-miRNAs). Pairwise correlation between biomarkers. Colored squares represent the amount of Pearson correlation within each pair of variables.

Table 3. Sensitivity and specificity of predictive variables associated with MPM.

Biomarker	TP	TN	Sensitivity (%)	Specificity (%)	AUC (95% CI)
Mesothelin	20	43	77	80	0.88 (0.79, 0.96)
Fibulin-3	23	47	88	87	0.94 (0.87, 1.0)
HMGB1	24	43	92	80	0.92 (0.86, 0.97)
hsa-miR-30e-3p	16	42	62	78	0.81 (0.71, 0.91)
hsa-miR-103a-3p	22	32	85	59	0.81 (0.71, 0.91)
hsa-miR-30e-3p hsa-miR-103a-3p	21	42	81	78	0.90 (0.83, 0.98)
Mesothelin HMGB1	22	47	85	87	0.94 (0.89, 1.0)
Fibulin-3 HMGB1	24	46	92	85	0.95 (0.91, 1.0)
Mesothelin Fibulin-3	24	49	92	91	0.98 (0.97, 1.0)
Mesothelin Fibulin-3 HMGB1	25	50	96	93	0.99 (0.97, 1.0)

TP: True positives; TN: true negatives; AUC, Area Under the Curve; CI, confidence interval.

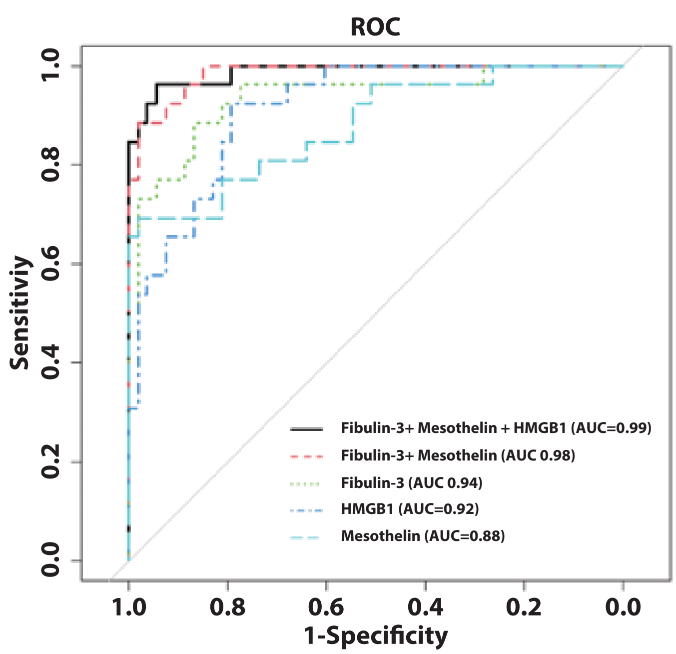

Figure 2. ROC curves of the three most discriminating biomarkers taken alone (i.e., HMGB1, Fibulin-3, and Mesothelin) and in combination (i.e., Mesothelin+Fibulin-3+HMGB1, and Mesothelin+Fibulin-3). Models were adjusted for sex, age, smoking habits, and BMI.

4. Discussion

MPM is a rare malignant tumor strongly associated with asbestos exposure. It is characterized by poor prognosis, and diagnosis is based on invasive techniques. In such a scenario, there is a need to identify reliable non-invasive early biomarkers in subjects at high risk. In particular, an increasing number of studies have explored using different biomarker panels to overcome the poor sensitivity and specificity of single markers and improve the predictive disease power in a diagnostic setting [15].

In the current study, we measured the Mesothelin, Fibulin-3, and HMGB1 protein biomarkers and the two hsa-miR-30e-3p and hsa-miR-103a-3p EV-miRNA and assessed their ability, alone and in combination, to discriminate between 26 MPM and 54 PAE subjects.

Mesothelin is the most studied diagnostic molecular biomarker for MPM [28]. Generally, it is expressed at low levels by normal mesothelial cells while it is overexpressed both in the membrane-bound- and in the soluble form in different cancers, such as MPM, ovarian, and lung cancers [29]. To assess plasmatic mesothelin levels, we used the ELISA technique taking advantage of the MesoMark assay, as did most of the studies in the field [15]. As reported in the literature, we detected higher concentrations of plasmatic mesothelin in MPM compared to healthy PAE subjects. Although Mesothelin showed a good discrimination power (AUC 0.88) between cases and controls, sensitivity and specificity were quite low. Our findings are consistent with previous case-control studies comparing MPM with PAE subjects [30-32].

We also investigated Fibulin-3, a secreted glycoprotein able to promote tumor growth by modulation of the AKT signaling pathway [33]. Plasmatic Fibulin-3 levels were higher in MPM than in PAE subjects, and concentrations were comparable to those previously reported by Pass and colleagues [34]. However, Fibulin-3 concentrations reported in the literature are inconsistent [32, 35], probably due to the lack of standardization of sample storage and different Fibulin-3 detection methods [36]. The diagnostic ability to circulate Fibulin-3 is also controversial, as studies conducted in North American, Chinese, Turkish, and Egyptian populations were strongly supportive [34, 37-39], while other conducted in European and Australian populations reported low diagnostic performance and discrimination ability, in particular with non-MPM malignancies [40, 41]. In the present study, Fibulin-3 showed the highest discriminating ability as a single biomarker, and our results are coherent with a previous study conducted by Pass and colleagues on 92 MPM and 136 PAE subjects (AUC 0.98) [34]. However, a recent meta-analysis conducted by Pei and colleagues reported lower pooled sensitivity (62%) and specificity (82%) than those observed in the present study [36]. Further validation studies in large populations, including groups with non-MPM malignancies, and standardization of detection methods are needed to overcome the inconsistencies and evaluate the actual reliability of circulating Fibulin-3 as a diagnostic biomarker for MPM.

HMGB1 protein is a damage-associated molecular pattern protein released in the extracellular space during necrosis, leading to chronic inflammation [42-44]. This circulating protein is involved in tumorigenesis and is known to be actively secreted by transformed MPM cells [42, 45, 46]. We observed a higher concentration of circulating HMGB1 in MPM and a good discriminating ability with an AUC of 0.92 (0.86, 0.97), a sensitivity of 92%, and a specificity of 80%. To our knowledge, we were the first to investigate HMGB1 in plasma samples [15, 32] The results obtained are similar to what was reported in the literature for HMGB1 serum concentrations [42, 47, 48], thus indicating plasma as a suitable biological fluid for the detection of this biomarker. In particular, Napolitano and colleagues reported an AUC of 0.83 with very high specificity (100%) and a sensitivity of 72% [42] and suggested that the hyper-acetylated form of HMGB1 had higher performance. However, a recent concern cast doubt on the validity of data on the hyper-acetylated form of the protein [49].

On the other hand, the study of Ying and colleagues reported an AUC of 0.94 with a lower specificity of 57% and the highest sensitivity of 100% [47]. The inconsistencies observed might be due to the different detection methods applied. Indeed, while the group of Napolitano and colleagues took advantage of the mass spectrometry technique, the group of Ying and colleagues and ours used the ELISA detection method. Moreover, some studies reported no significant differences between patients with MPM and patients with other non-MPM malignancies or asbestosis [47, 48]. Further studies with particular attention to the standardization of analysis methods are needed to define the actual discriminating ability to circulate HMGB1.

None of the tested biomarkers showed significant differences when we considered the TNM stages and histotype. However, the small number of subjects in each category prevents any firm conclusion.

In recent years, the use of circulating miRNAs for MPM diagnosis has been widely explored, and several studies reported specific miRNA signatures related to MPM diagnosis and prognosis [12, 16, 50, 51]. miRNAs are small noncoding RNAs involved in regulating gene expression and modulation of various cellular functions, such as proliferation, differentiation, and invasion [52, 53]. In the present and our previous study, we specifically focused on circulating EV-associated miRNA expression, as they are emerging as an active mechanism of communication between cells. Thus, we hypothesized they might reflect the active crosstalk between cancer and the immune system rather than a passive release in the extracellular environment. We previously identified the specific two-EV-miRNA signature miR-103a-3p and miR-30e-3p that was able to discriminate between patients with MPM and PAE subjects, with an AUC of 0.94 (95%CI 0.87±1.00), a sensitivity of 96% and a specificity of 80% [20]. In the current study, the two-EV-miRNA signature generated an AUC of 0.90, but the sensitivity and specificity were lower than those observed in our previous study.

Since combining different biomarkers has been encouraged to set diagnostic tools with higher accuracy [12, 15, 42, 49], we tested different combinations of the biomarkers examined in the present study. As the discrimination ability of the two EV-miRNA-panel resulted lower than that of Fibulin-3 and HMGB1 even taken alone, we considered only Mesothelin, Fibulin-3, and HMGB1 and observed that in combination, they showed the highest discriminating ability (AUC of 0.99), sensitivity (96%), and specificity (93%). The present study is the first one that evaluated the combination of plasmatic Mesothelin, Fibulin-3, and HMGB1 biomarkers together. In a previous study, plasmatic Mesothelin, Calretinin, and the Megakaryocyte potentiating factor generated an AUC of 0.94 in a population of 128 males (sensitivity 82%, specificity 95%), and AUC of 0.94 in a population of 38 females compared to healthy controls (sensitivity 87%, specificity 95%) [54], thus showing a lower discriminating potential than that of the panel tested in the current study. When we evaluated the combination only of Mesothelin and Fibulin-3, the AUC did not differ, but a lower sensitivity was detected. Thus, the actual improvement conferred by HMGB1 to the Mesothelin and Fibulin-3 panel needs to be confirmed in a larger study. In their recent meta-analysis, Schillebeeckx et al. encourage to focus on external validation of already identified biomarkers and biomarker panels, indicating Mesothelin, Fibulin-3, and HMGB1 as the most promising biomarkers for MPM detection with translational potential to the routine clinical practice [15].

Other studies have explored using plasmatic biomarker panels, in particular, combining Mesothelin with different markers to improve the discriminating potential in a diagnostic setting. In particular, Weber and colleagues combined Mesothelin with mir103a-3p in a study including 43 MPM and 52 PAE and observed an increased diagnostic performance (AUC 0.90, sensitivity 95%, specificity 81%) compared to the single biomarkers (mesothelin: AUC 0.81, sensitivity 74%, specificity 85%; miR-103-ap AUC 0.76, sensitivity 89%, specificity 81%).

We acknowledge some limitations of the present study. First, the small number of subjects and the lack of subjects with other respiratory diseases (e.g., lung cancer, benign pleural effusion, asbestosis) prevent definite conclusions. Second, we acknowledge that MPM patients showed a slightly unhealthy metabolic profile (more smokers, higher BMI, and older age). However, we considered these variables in the statistical analyses to assess the independent role of the tested biomarkers on the odds of being a patient with MPM. Moreover, as an explorative study, we did not perform an independent validation for the combined biomarkers. Thus, validation studies are needed in larger populations to confirm the results described.

5. Conclusions

The combination of the three plasmatic Mesothelin, Fibulin-3, and HMGB1 biomarkers showed the highest discrimination ability between MPM patients and PAE subjects and appears to be a promising high-specificity biomarker panel for MPM diagnosis.

Despite the high number of studies that evaluated previously identified and new potential biomarkers, none of them can be considered sufficiently reliable to be used in the surveillance of asbestos-exposed subjects or the early diagnosis of MPM. As underlined by the recent ERS/ESTS/EACTSD/ESTR European guidelines for the management of MPM: "routine determination of previously proposed biomarkers in MPM has no current validated role in diagnosis, prognosis or clinical follow-up (disease monitoring)" [1]. The rarity of the disease, even in cohorts of asbestos-exposed subjects, and the lack of clear evidence of effective treatments leading to survival improvements (reduction of mortality) in early-diagnosed cases are other factors hampering the use of the biomarkers described so far. Even their possible application as diagnostic biomarkers to guide the selection of those subjects needing further investigations for early detection of the disease remains controversial.

However, several authors, including Scherpereel et al., in the ERS/ESTS/EACTSD/ESTR guidelines [1], encouraged further research into the role of biomarkers. Further case-control validation studies have to be conducted in larger populations, including subjects with other non-MPM malignancies, and prospective longitudinal studies to confirm the evidence observed. The results obtained in the present study contribute to identifying new potential non-invasive biomarkers for future validation studies.

Supplementary materials: Supplementary Table S1: Geometric means of biomarkers in the four TNM stages; Supplementary Table S2: Geometric means of biomarkers in the three histotypes; Supplementary Table S3: Univariate logistic regression of protein, miRNA, and covariates estimating the odds of MPM; Supplementary Table S4: multiple logistic regression estimating the odds of MPM; Supplementary Table S5: ROC comparisons.

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Informed consent statement: All participants provided signed written informed consent. The study design, research aims, and measurements were approved by the Ethics Committee "Comitato Etico - Milano Area 2" of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy (approval number #2423), in agreement with principles of the Helsinki Declaration. MPM patients were followed-up in June 2021 to ascertain their vital status.

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Declaration of interest: Carolina Mensi served as a consultant for the court and patients in litigations concerning asbestos-related diseases. The other authors declare no conflicts of interest.

References

1. Scherpereel A, Opitz I, Berghmans T, et al. ERS/ESTS/EACTS/ESTRO guidelines for the management of malignant pleural mesothelioma. *Eur Respir J*. 2020;55(6):1900953. Doi:10.1183/13993003.00953-2019
2. Fazzo L, Binazzi A, Ferrante D, et al. Burden of Mortality from Asbestos-Related Diseases in Italy. *Int J Environ Res Public Health*. 2021;18(19):10012. Doi:10.3390/IJERPH181910012
3. International Agency for Research on Cancer (IARC). Mesothelioma. Mesothelioma Globocan 2020. Published 2022. Accessed April 14, 2022. https://gco.iarc.fr/today/data/factsheets/cancers/18-Mesothelioma-fact-sheet.pdf
4. Binazzi A, Marzio D Di, Verardo M, et al. Asbestos Exposure and Malignant Mesothelioma in Construction Workers-Epidemiological Remarks by the Italian National Mesothelioma Registry (ReNaM). *Int J Environ Res Public Heal*. 2022;19:235. Doi:10.3390/ijerph19010235
5. Schumann SO, Kocher G, Minervini F. Epidemiology, diagnosis and treatment of the malignant pleural mesothelioma, a narrative review of literature. *J Thorac Dis*. 2021;13(4):2510-2523. Doi:10.21037/JTD-20-2761
6. Bianco A, Valente T, de Rimini ML, Sica G, Fiorelli A. Clinical diagnosis of malignant pleural mesothelioma. *J Thorac Dis*. 2018;10(Suppl2):S253-S261. Doi:10.21037/JTD.2017.10.09
7. Wu YB, Xu LL, Wang XJ, et al. Diagnostic value of medical thoracoscopy in malignant pleural effusion. *BMC Pulm Med*. 2017;17(1):109. Doi:10.1186/S12890-017-0451-1

8. Cinausero M, Rihawi K, Cortiula F, Follador A, Fasola G, Ardizzoni A. Emerging therapies in malignant pleural mesothelioma. *Crit Rev Oncol Hematol*. 2019;144:102815. Doi:10.1016/J.CRITREVONC.2019.102815
9. Davis A, Ke H, Kao S, Pavlakis N. An Update on Emerging Therapeutic Options for Malignant Pleural Mesothelioma. *Lung Cancer (Auckland, NZ)*. 2022;13:1-12. Doi:10.2147/LCTT.S288535
10. Tsao AS, Pass HI, Rimner A, Mansfield AS. New Era for Malignant Pleural Mesothelioma: Updates on Therapeutic Options. *J Clin Oncol*. 2022;40(6):681-692. Doi:10.1200/JCO.21.01567
11. Cavallari I, Urso L, Sharova E, Pasello G, Ciminale V. Liquid Biopsy in Malignant Pleural Mesothelioma: State of the Art, Pitfalls, and Perspectives. *Front Oncol*. 2019;9(AUG):740. Doi:10.3389/FONC.2019.00740
12. Ferrari L, Carugno M, Mensi C, Pesatori AC. Circulating Epigenetic Biomarkers in Malignant Pleural Mesothelioma: State of the Art and critical Evaluation. *Front Oncol*. 2020;10:445. Doi:10.3389/FONC.2020.00445
13. Poulet G, Massias J, Taly V. Liquid Biopsy: General Concepts. *Acta Cytol*. 2019;63(6):449-455. Doi:10.1159/000499337
14. Armato SG, Nowak AK, Francis RJ, et al. Imaging in pleural mesothelioma: A review of the 15th International Conference of the International Mesothelioma Interest Group. *Lung Cancer*. 2022;164:76-83. Doi:10.1016/J.LUNGCAN.2021.12.008
15. Schillebeeckx E, van Meerbeeck JP, Lamote K. Clinical utility of diagnostic biomarkers in malignant pleural mesothelioma: a systematic review and meta-analysis. *Eur Respir Rev*. 2021;30(162):210057. Doi:10.1183/16000617.0057-2021
16. Tomasetti M, Amati M, Neuzil J, Santarelli L. Circulating epigenetic biomarkers in lung malignancies: From early diagnosis to therapy. *Lung Cancer*. 2017;107:65-72. Doi:10.1016/J.LUNGCAN.2016.05.023
17. van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. *Nat Rev Mol Cell Biol*. 2018;19(4):213-228. Doi:10.1038/nrm.2017.125
18. Shah R, Patel T, Freedman JE. Circulating extracellular vesicles in human disease. *N Engl J Med*. 2018;379:958-966. Doi:10.1056/NEJMra1704286
19. Lucchetti D, Ricciardi Tenore C, Colella F, Sgambato A. Extracellular Vesicles and Cancer: A Focus on Metabolism, Cytokines, and Immunity. *Cancers (Basel)*. 2020;12(1):171. Doi:10.3390/cancers12010171
20. Cavalleri T, Angelici L, Favero C, et al. Plasmatic extracellular vesicle microRNAs in malignant pleural mesothelioma and asbestos-exposed subjects suggest a 2-miRNA signature as potential biomarker of disease. *PLoS One*. 2017;12(5):e0176680. Doi:10.1371/JOURNAL.PONE.0176680
21. Nowak AK, Chansky K, Rice DC, et al. The IASLC Mesothelioma Staging Project: Proposals for Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Pleural Mesothelioma. *J Thorac Oncol*. 2016;11(12):2089-2099. Doi:10.1016/J.JTHO.2016.08.147
22. Rice D, Chansky K, Nowak A, et al. The IASLC Mesothelioma Staging Project: Proposals for Revisions of the N Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Pleural Mesothelioma. *J Thorac Oncol*. 2016;11(12):2100-2111. Doi:10.1016/J.JTHO.2016.09.121
23. Pass H, Giroux D, Kennedy C, et al. The IASLC Mesothelioma Staging Project: Improving Staging of a Rare Disease Through International Participation. *J Thorac Oncol*. 2016;11(12):2082-2088. Doi:10.1016/J.JTHO.2016.09.123
24. Marinaccio A, Binazzi A, Marzio D Di, et al. Pleural malignant mesothelioma epidemic: incidence, modalities of asbestos exposure and occupations involved from the Italian National Register. *Int J cancer*. 2012;130(9):2146-2154. Doi:10.1002/IJC.26229
25. Weber DG, Casjens S, Johnen G, et al. Combination of MiR-103a-3p and Mesothelin Improves the Biomarker Performance of Malignant Mesothelioma Diagnosis. Altomare DA, ed. *PLoS One*. 2014;9(12):e114483. Doi:10.1371/journal.pone.0114483
26. Tsim S, Alexander L, Kelly C, et al. Serum Proteomics and Plasma Fibulin-3 in Differentiation of Mesothelioma From Asbestos-Exposed Controls and Patients With Other Pleural Diseases. *J Thorac Oncol*. 2021;16(10):1705-1717. Doi:10.1016/j.jtho.2021.05.018
27. Handke N, Rupp A, Trimpop N, von Pawel J, Holdenrieder S. Soluble High Mobility Group Box 1 (HMGB1) Is a Promising Biomarker for Prediction of Therapy Response and Prognosis in Advanced Lung Cancer Patients. *Diagnostics*. 2021;11(2):356. Doi:10.3390/diagnostics11020356
28. Corradi M, Goldoni M, Alinovi R, et al. YKL-40 and mesothelin in the blood of patients with malignant mesothelioma, lung cancer and asbestosis. *Anticancer Res*. 2013;33(12):5517-5524.
29. Tang Z, Qian M, Ho M. The role of mesothelin in tumor progression and targeted therapy. *Anticancer Agents Med Chem*. 2013;13(2):276-280. Doi:10.2174/1871520611313020014
30. Chen Z, Gaudino G, Pass HI, Carbone M, Yang H. Diagnostic and prognostic biomarkers for malignant mesothelioma: an update. *Transl lung cancer Res*. 2017;6(3):259-269. Doi:10.21037/TLCR.2017.05.06
31. Cristaudo A, Bonotti A, Guglielmi G, Fallahi P, Foddis R. Serum mesothelin and other biomarkers: what have we learned in the last decade? *J Thorac Dis*. 2018;10(Suppl2):S353-S359. Doi:10.21037/JTD.2017.10.132
32. Pass HI, Alimi M, Carbone M, Yang H, Goparaju CM. Mesothelioma Biomarkers: A Review Highlighting Contributions from the Early Detection

Research Network. *Cancer Epidemiol Biomarkers Prev*. 2020;29(12):2524-2540. Doi:10.1158/1055-9965.EPI-20-0083

33. Hwang CF, Chien CY, Huang SC, et al. Fibulin-3 is associated with tumour progression and a poor prognosis in nasopharyngeal carcinomas and inhibits cell migration and invasion via suppressed AKT activity. *J Pathol*. 2010;222(4):367-379. Doi:10.1002/PATH.2776
34. Pass HI, Levin SM, Harbut MR, et al. Fibulin-3 as a blood and effusion biomarker for pleural mesothelioma. *N Engl J Med*. 2012;367(15):1417-1427. Doi:10.1056/NEJMOA1115050
35. Creaney J, Dick IM, Robinson BW. Comparison of mesothelin and fibulin-3 in pleural fluid and serum as markers in malignant mesothelioma. *Curr Opin Pulm Med*. 2015;21(4):352-356. Doi:10.1097/MCP.0000000000000167
36. Pei D, Li Y, Liu X, et al. Diagnostic and prognostic utilities of humoral fibulin-3 in malignant pleural mesothelioma: Evidence from a meta-analysis. *Oncotarget*. 2017;8(8):13030-13038. Doi:10.18632/ONCOTARGET.14712
37. Kaya H, Demir M, Taylan M, et al. Fibulin-3 as a diagnostic biomarker in patients with malignant mesothelioma. *Asian Pac J Cancer Prev*. 2015;16(4):1403-1407. Doi:10.7314/APJCP.2015.16.4.1403
38. Hassan MH, Abuhamdah S, Abdel-Bary M, et al. Circulating and local nuclear expression of survivin and fibulin-3 genes in discriminating benign from malignant respiratory diseases: correlation analysis. *Biosci Rep*. 2021;41(1):BSR20203097. Doi:10.1042/BSR20203097
39. Jiang Z, Ying S, Shen W, et al. Plasma Fibulin-3 as a Potential Biomarker for Patients with Asbestos-Related Diseases in the Han Population. *Dis Markers*. 2017;2017:1725354 Doi:10.1155/2017/1725354
40. Creaney J, Dick IM, Meniawy TM, et al. Comparison of fibulin-3 and mesothelin as markers in malignant mesothelioma. *Thorax*. 2014;69(10):895-902. Doi:10.1136/thoraxjnl-2014-205205
41. Kirschner MB, Pulford E, Hoda MA, et al. Fibulin-3 levels in malignant pleural mesothelioma are associated with prognosis but not diagnosis. *Br J Cancer*. 2015;113(6):963-969. Doi:10.1038/BJC.2015.286
42. Napolitano A, Antoine DJ, Pellegrini L, et al. HMGB1 and Its Hyperacetylated Isoform are Sensitive and Specific Serum Biomarkers to Detect Asbestos Exposure and to Identify Mesothelioma Patients. *Clin Cancer Res*. 2016;22(12):3087-3096. Doi:10.1158/1078-0432.CCR-15-1130
43. Yang H, Rivera Z, Jube S, et al. Programmed necrosis induced by asbestos in human mesothelial cells causes high-mobility group box 1 protein release and resultant inflammation. *Proc Natl Acad Sci U S A*. 2010;107(28):12611-16. Doi:10.1073/PNAS.1006542107/-/DCSUPPLEMENTAL/PNAS.201006542SI.PDF
44. Wang S, Zhang Y. HMGB1 in inflammation and cancer. *J Hematol Oncol*. 2020;13(1):1-4. Doi:10.1186/S13045-020-00950-X/FIGURES/1
45. Jube S, Rivera ZS, Bianchi ME, et al. Cancer cell secretion of the DAMP protein HMGB1 supports progression in malignant mesothelioma. *Cancer Res*. 2012;72(13):3290-3301. Doi:10.1158/0008-5472.CAN-11-3481
46. Mezzapelle R, De Marchis F, Passera C, et al. CXCR4 engagement triggers CD47 internalization and antitumor immunization in a mouse model of mesothelioma. *EMBO Mol Med*. 2021;13(6):e12344. Doi:10.15252/EMMM.202012344
47. Ying S, Jiang Z, He X, et al. Serum HMGB1 as a Potential Biomarker for Patients with Asbestos-Related Diseases. *Dis Markers*. 2017;2017:5756102. Doi:10.1155/2017/5756102
48. Tabata C, Shibata E, Tabata R, et al. Serum HMGB1 as a prognostic marker for malignant pleural mesothelioma. *BMC Cancer*. 2013;13(1):1-6. Doi:10.1186/1471-2407-13-205/FIGURES/3
49. Napolitano A, Antoine DJ, Pellegrini L, et al. Expression of Concern: HMGB1 and Its Hyperacetylated Isoform are Sensitive and Specific Serum Biomarkers to Detect Asbestos Exposure and to Identify Mesothelioma Patients. *Clin Cancer Res*. 2020;26(6):1529. Doi:10.1158/1078-0432.CCR-20-0338
50. Han YQ, Xu SC, Zheng WQ, Hu Z De. Diagnostic value of microRNAs for malignant pleural mesothelioma: A mini-review. *Thorac cancer*. 2021;12(1):8-12. Doi:10.1111/1759-7714.13746
51. Martínez-Rivera V, Negrete-García MC, Ávila-Moreno F, Ortiz-Quintero B. Secreted and tissue miRNAs as diagnosis biomarkers of malignant pleural mesothelioma. *Int J Mol Sci*. 2018;19(2):595. Doi:10.3390/ijms19020595
52. Filipów S, Łaczmański Ł. Blood Circulating miRNAs as Cancer Biomarkers for Diagnosis and Surgical Treatment Response. *Front Genet*. 2019;10(FEB):169. Doi:10.3389/FGENE.2019.00169
53. Goodall GJ, Wickramasinghe VO. RNA in cancer. *Nat Rev Cancer*. 2021;21(1):22-36. Doi:10.1038/S41568-020-00306-0
54. Jiménez-Ramírez C, Casjens S, Juárez-Pérez CA, et al. Mesothelin, Calretinin, and Megakaryocyte Potentiating Factor as Biomarkers of Malignant Pleural Mesothelioma. *Lung*. 2019;197(5):641-649. Doi:10.1007/S00408-019-00244-1

Appendix: Supplementary material

Supplementary Table S1. Geometric means of biomarkers in the four TNM stages.

Biomarker	TNM stage	Geometric Mean	LCI	UCI	p-value of comparisons	Overall p-value
HMGB1	I	11.9	7.3	19.3	Reference	0.317
	II	9.5	5.4	16.7	0.542	
	III	6.5	3.8	10.8	0.090	
	IV	11.6	6.3	21.5	0.957	
Fibulin-3	I	53.9	44.8	64.9	Reference	0.854
	II	48.5	39.2	60.1	0.446	
	III	53.9	44.2	65.7	0.997	
	IV	51.2	40.5	64.7	0.722	
Mesothelin	I	2.0	0.9	4.7	Reference	0.974
	II	2.2	0.8	5.8	0.893	
	III	2.2	0.9	5.3	0.911	
	IV	1.6	0.6	4.8	0.754	
hsa-miR-103a-3p	I	435.6	87.2	2176.8	Reference	0.745
	II	217.1	38.2	1234.1	0.547	
	III	191.7	38.4	958.1	0.462	
	IV	120.3	17.9	807.5	0.295	
hsa-miR-30e-3p	I	294.8	63.0	1379.8	Reference	0.620
	II	125.0	23.6	662.3	0.441	
	III	92.6	19.8	433.2	0.282	
	IV	75.5	12.2	469.0	0.250	

LCI; lower 95% confidence interval; UCI: upper 95% confidence interval; tissue specimens were classified according to the TNM staging system established by IMIG and IASLC.

Supplementary Table S2. Geometric means of biomarkers in the three histotypes.

Biomarker	Histology	Geometric Mean	LCI	UCI	p-value of comparisons	Overall p-value
HMGB1	Epithelioid	10.6	6.7	16.7	Reference	0.815
	Biphasic	9.7	3.5	26.9	0.528	
	Sarcomatoid	8.8	6.0	12.9	0.851	
Fibulin-3	Epithelioid	52.1	44.2	61.4	Reference	0.995
	Biphasic	53.0	36.7	76.5	0.988	
	Sarcomatoid	52.0	45.2	59.7	0.921	
Mesothelin	Epithelioid	2.2	1.1	4.6	Reference	0.830
	Biphasic	1.3	0.3	6.7	0.843	
	Sarcomatoid	2.0	1.1	3.7	0.609	
hsa-miR-103a-3p	Epithelioid	214.3	57.5	798.5	Reference	0.569
	Biphasic	964.4	50.9	18269.7	0.884	
	Sarcomatoid	189.1	59.7	599.5	0.297	
hsa-miR-30e-3p	Epithelioid	154.1	42.6	557.9	Reference	0.661
	Biphasic	363.1	20.4	6449.8	0.610	
	Sarcomatoid	100.5	32.5	310.6	0.398	

LCI; lower 95% Confidence Interval; UCI: upper 95% Confidence Interval.

Supplementary Table S3. Univariate logistic regression of protein, miRNA, and covariates estimating the odds of MPM.

Variable	Estimate	SE	p-value	OR	LCI	UCI
hsa-miR-103a-3p	0.0000	0.0001	0.726	0.99996	0.99970	1.000
hsa-miR-30e-3p	0.0000	0.0003	0.873	1.00004	0.99950	1.001
Mesothelin	1.3458	0.4244	0.002	3.841	1.672	8.826
Fibulin-3	0.2607	0.0733	0.000	1.298	1.124	1.498
HMGB1	0.1749	0.0582	0.003	1.191	1.063	1.335
Age	0.144	0.042	0.001	1.155	1.064	1.253
BMI	-0.132	0.065	0.044	0.876	0.771	0.996
Gender M vs F	0.350	0.309	0.256	2.014	0.601	6.752
Smoking habits YES vs NO	0.196	0.517	0.705	1.875	0.364	9.643
Smoking habits Former vs Never	0.237	0.355	0.504	1.953	0.701	5.440

SE: standard error; OR: Odds Ratio; LCI; lower 95% Confidence Interval; UCI: upper 95% Confidence interval.

Supplementary Table S4. Multiple logistic regression estimating the odds of MPM.

Outcome: MPM	Estimate	SE	p-value	OR	LCI	UCI
Mesothelin	1.14	0.60	0.058	3.13	0.96	10.16
Fibulin-3	0.69	0.29	0.017	2.00	1.14	3.53
HMGB1	0.24	0.13	0.055	1.27	1.00	1.63
Smoking habits YES vs No	-4.03	2.44	0.099	0.02	<0.001	2.13
Smoking habits Former vs No	-3.10	3.02	0.304	0.05	<0.001	16.69
Age	0.45	0.22	0.040	1.57	1.02	2.41
BMI	-0.28	0.15	0.070	0.76	0.56	1.02
gender M vs F	-5.94	3.60	0.099	0.00	<0.001	3.03

OR: Odds ratio; lower 95% Confidence Interval; UCI: upper 95% confidence interval. Models adjusted for gender, age, smoking habits, and BMI.

Supplementary Table S5. ROC comparisons.

ROC comparisons	Estimate ROC difference	SE	LCI	UCI	p-value
Fibulin-3 Mesothelin HMGB1 Vs Fibulin-3 Mesothelin	0.003	0.008	-0.012	0.018	0.674
hsa-miR-30e-3p hsa-miR-103 Vs Fibulin-3 Mesothelin	-0.086	0.036	-0.156	-0.017	0.015

SE: standard error; LCI: lower 95% Confidence Interval; UCI: upper 95% Confidence Interval. Comparison of models adjusted for gender, age, smoking habits, and BMI.

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Effectiveness of prevention of SARS-CoV-2 transmission among unvaccinated Italian healthcare workers

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Keywords: COVID-19; SARS-CoV-2; occupational safety; personal protective equipment; mask; health care workers; risk assessment; public health

Abstract

Background: *We aimed to investigate the association between personal protective equipment (PPE) use and SARS-CoV-2 infection among healthcare workers (HCWs).* **Methods:** *We analyzed occupational surveillance contact forms followed by a PCR test notified between March and September 2020 by Italian HCWs. The odds ratios (ORs) and 95% Confidence Intervals (CIs) for positive PCR based on HCWs and contacts characteristics were calculated through multivariable logistic regression models. When multiple contacts were potentially effective for a PCR test, they were weighted by the inverse of their number.* **Results:** *Overall, 4,883 contacts reported by 2,952 HCWs were analyzed, and 224 contacts among 144 HCWs had positive PCR. No difference was found according to sex, age, employment, or job title, except for an OR of 0.30 (95%CI 0.11-0.78) for resident physicians, compared to administrative staff. The ORs for use of surgical mask were 0.59 (95%CI=0.40-0.86) for use only by HCW, 0.49 (95%CI=0.22-1.07) only by the infected person, and 0.40 (95%CI=0.27-0.60) by both, compared to use by neither. Use of other PPEs was not associated with infection, while the OR for hand sanitation was 0.61 (95%CI=0.40-0.93). HCWs reporting fever, cough, and asthenia had a higher risk of infection.* **Conclusions:** *Use of surgical masks was associated with a 40-60% lower risk of infection, especially when both HCWs and infected individuals used them. Our results quantify the role played by mask use and hand sanitation in preventing SARS-CoV-2 transmission in high-risk circumstances.*

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1. Introduction

To date, increasing evidence on the epidemiology of SARS-CoV-2 infection has risen worldwide. Particular attention has been given to health-care workers (HCWs) due to their higher probability of exposure. Before the introduction of vaccines, the use of personal protection equipment (PPE) has represented an important means to decrease the risk of transmission of the virus.

Available studies [1] provide evidence of efficacy against infection for masks, gowns, eye protection, and handwashing, including a dose-response relationship between adequate use of PPE and risk REDUCTION. Despite its ascertained benefit in preventing SARS-CoV-2 transmission, the effectiveness of the use of masks has not been precisely characterized, as it depends on idiosyncratic circumstances which may be difficult to take into account [2]. Besides this, reuse of PPE is common, and additionally the prolonged wearing of PPE has been associated with adverse effects like heat, thirst, and pressure areas up to exhaustion [3].

When infection started to spread in Italian hospitals, surveillance systems were set up to monitor its diffusion, with occupational medicine units involved in its control among the HCWs. We previously reported the results of a pooled analysis of data from occupational surveillance from six different Italian centers, including a subset of the present study population (843 infections diagnosed between March and May 2020) [4]. In that study, infection was more common among men, and mask used by the infected contact was an independent protective factor, while we found no difference based on job title or working department. Another large cohort study conducted in China described a higher risk of SARS-CoV-2 transmission for severe index cases, and reported a ten-fold higher risk for acquired infection in the household compared to the hospital setting, which may be explained by more frequent and longer unprotected exposure in the former and by mandatory use of mask and the high perceived risk within in the latter [5]. Since transmission can occur before symptoms' onset, a single infection can lead to multiple unprotected contacts before being diagnosed [6].

At the beginning of the pandemic, the Occupational Medicine Unit of Turin's University Hospital, set up a health surveillance program to identify infected HCWs, and to isolate and monitor them according to the public health regulations of the time. All HCWs were asked to notify each contact with a COVID-19 case. Risk assessment was performed to individuate those contacts possibly at risk and needing a diagnostic test.

This study aims to investigate the association between PPE use and SARS-CoV-2 infection among HCWs during the first wave of the SARS-CoV-2 pandemic, when vaccines were not available, and knowledge about the infection as well as guidelines for handling potential occupational contacts were rapidly developing.

2. Methods

We conducted a cross-sectional study on SARS-CoV-2 infection focusing on the use of PPEs and other characteristics among HCWs. Data were collected by the occupational medicine unit of the University Hospital of Turin, Northern Italy, from late February to September 2020. Surveillance systems, including contact tracing and monitoring of infected subjects, were established within the hospital in order to monitor HCWs for possible infection with SARS-CoV-2. Testing for infection was set up with rhino-pharyngeal swabs to detect SARS-CoV-2 RNA by RT-PCR, in a reference laboratory, and databases were established to monitor and follow subjects. SARS-CoV-2 RNA was studied by a molecular test, AptimaTM SARS-CoV-2 Assay with the PantherTM Fusion System (Hologic, Rome, Italy) [7]. The assay combines the technologies of target capture, Transcription Mediated Amplification, and Dual Kinetic Assay and detects two conserved regions of the ORF1ab gene. Qualitative results were determined by a cut-off based on the total Relative Light Units and the kinetic curve type. No information on viral load was available. Samples were analyzed according to the guidelines proposed by the World Health Organization. Risk assessment was performed for each contact reported by HCWs, and additional PCR tests were prescribed based on it.

The first risk management protocol was established on March 6th, 2020, four days after the first index case in Turin. Before standardizing the procedure, when epidemiological criteria were poorly defined (i.e., emphasis was on return from endemic areas), information on suspected cases was collected from wards and transmitted in different ways to the occupational medicine unit. With the exponential increase of cases, the risk management protocols evolved, and with them, the forms used to notify the contacts. On April 10th, reporting procedures were shifted into a dedicated platform; this reduced significantly missing data, filling errors, accelerated risk assessment, and further communication to the HCW [8].

Risk management protocol indications for PCR test included: (i) suspected symptoms (fever defined as a temperature higher than 37.5 °C, dry cough of recent onset, dyspnea or minimum two symptoms among sore throat, severe asthenia, ageusia/hypogeusia, anosmia/hyposmia, headache, diarrhea/nausea/vomit, bilateral conjunctivitis, rhinorrhea), or (ii) at-risk contact, defined as not fully protected contact (surgical mask or facial respirator if aerosol exposed, glasses or visor, gloves or hand sanitization and gown) with a confirmed COVID-19 case for more than 15 minutes or at a distance of less than 2 meters.

The time schedules for PCR testing changed over time, but usually tests were performed at least 3 days after the contact at risk. A contact was considered at risk if it happened at least 48 hours before, and at maximum 14 days after the assessment of the infection.

Negative results were communicated by email, while positive results were communicated by phone call and an email containing information about self-isolation and return to work procedures. Quarantine of positive subjects ended when two consecutive negative tests were obtained.

The form used to collect surveillance data included: basic demographic information, job title, department of employment, self-reported circumstances of contact with a COVID-19 case, self-reported use of PPEs, and selected self-reported symptoms. Also, data were available for use of a surgical mask by the source of infection (patient or colleague). Contact forms were matched with the results of the PCR tests. Details on the timing of the contacts were derived from the date of contact notification.

The original dataset included more than 10,000 reporting forms. Contacts that filled the following conditions were considered potentially effective and retained in the analysis: (i) complete information on date of contact or date of infection of the source of contact, and date of PCR test; (ii) contact declared from 2 days before to 14 days after the date of a positive PCR test performed by the source of contact; (iii) PCR test performed by the HCW 2-14 days after the contact.

For HCW with at least one positive PCR test, only contacts potentially effective for the first positive PCR test were retained in the analysis; for HCW with only negative PCR tests, contacts potentially effective for all tests were included. When multiple contacts were potentially effective for a PCR test, they were weighted by the inverse of their number. For example, if a HCW reported two contacts qualifying to be effective (e.g., one 6 days and one 10 days before a PCR test), both contacts were retained in the analysis, each of them being weighted 0.5. For this reason, descriptive statistics of the contacts are presented only as percentages since the absolute numbers no longer correspond to individual contacts.

Multivariable weighted logistic regression models were employed to estimate the odds ratio (OR) and 95% Confidence Interval (CI) of effective contact for different predictors, which can be distinguished into subject-related and contact-related characteristics. The former group included sex, age, job title and department of employment; the latter group included use of PPEs, symptoms, and period and type of exposure related to the specific contact.

The main regression model included sex, age group, and job title as predictors. A sub-analysis using the same model was performed excluding the first 2 weeks of March. More complex models were estimated for variables regarding use of PPEs, symptoms, and period and type of exposure by adding a group of covariates, in turn, to this core set, based on backward selection.

The statistical package, STATA, Version 16, was used for the analysis [9].

3. Results

A total of 4,883 total contacts, reported by 2,952 different HCWs (average of 1.64 contacts per HCW) were retained in the analysis. Among these, we observed 224 (4.6%) effective individual contacts, i.e., contacts followed by a positive PCR test 2-14 days after COVID-19 contact occurrence, and 4,659 (95.4%) ineffective COVID-19 contacts, i.e., contacts reported by HCWs without any positive PCR test. A total of 144 (4.9%) individuals tested positive. Table 1 summarizes the main characteristics of the study population while the characteristics of the contacts are presented in Table 2.

Women represented 70.5% of HCWs included in the analysis, and the average age was 45.9 (range 23-70). The largest number of COVID-19 contacts were reported in the second half of March 2020 (n=1,832, 35%), corresponding also to the higher number of positive tests (n. 107), while the highest proportion of positive tests was reported between 1 and 15 March (13.5%).

Table 1. Main characteristics of the study population of health care workers*.

Characteristic	Number	%
Sex		
Male	866	29.5
Female	2,071	70.5
Age group		
20-35	654	22.1
36-50	1,107	37.5
51-70	1,191	40.4
Job title		
Physician	553	18.8
Resident physician	318	10.8
Nurse	1,190	40.4
Health assistant	461	15.6
Healthcare professional	270	9.2
Administrative staff/Other	151	5.1
Department		
Inpatients	1,956	67.9
Emergency room	328	11.2
Intensive care unit	165	5.6
COVID-19 unit	207	7.1
Total	2,952	100

**Numbers might not add to the total because of missing values.*

Overall, most HCWs reported wearing a mask during the contact (72.2%), while the source of infection did not (55.4%). Between 1 and 15 March 15, 41.4% of HCWs reported wearing a mask, against 76.9% in the second half of March 2020 and 79.3.0-85.6% during the following months. The source of infection was reported to wear the mask in 45.7% of the contacts; this proportion was 17.8% before 15 March, and between 37.6% and 61.9% in the following weeks. Most contacts occurred when the HCW was not wearing gloves (56.1%) or a face shield (83.1%). Additionally, we assessed the use of a mask by both the HCW and the source of infection for 4,807 contacts. In 22.6% of those, none was wearing a mask, 32.7% occurred with only the HCW wearing a mask, 5.1% with only the infected wearing a mask, and 39.6% with both wearing a mask. Despite the reported use of a mask by both subject and infected, 3.2% of these contacts resulted in a positive test. We observed no association between number of contacts notified and risk of infection. Among the symptoms declared by the HCWs, the most frequent were cough (10%), sore throat (6.5%), and fever (2.3%).

Table 3 shows the ORs of effective contact for sex, age, job title, PPE use, symptoms, and type of contact.

No associations were observed according to sex and age. When considering job title, resident physicians were less likely to report an effective contact (OR 0.30, 95%CI 0.11, 0.78, p=0.014) compared to administrative staff. Use of a mask by either the HCW (OR 0.63, 95%CI 0.45-0.87, p=0.006) and the source of infection (OR 0.63, 95%CI 0.45-0.89, p=0.008) was negatively associated with an effective contact.

Compared to contacts in which neither the HCW nor the source of infection wore a mask, the OR of positivity for contacts in which both wore a mask was 0.40 (95%CI 0.27-0.60). The use of a filtering facepiece 2 or 3 (FFP2/FFP3) mask was not common and resulted in an OR equal to 0.48, (95%CI 0.21-1.09). Women were 16% more likely

Table 2. Characteristics of contacts (Total number of contacts=4,883, 100%).

	Effective contacts* (%)	Ineffective contacts* (%)	Percentage of contacts over the total for each category
Time period of contact			
1 March - 15 March 2020	13.5	86.4	15.7
16 March - 31 March 2020	5.3	94.7	35.0
1 April - 15 April 2020	2.0	98.0	23.6
16 April - 30 April 2020	2.4	97.6	11.5
1 May - 30 September 2020	0.9	99.1	14.2
Use of PPEs (HCW)			
Surgical mask	4.0	96.0	72.2
FFP2/FFP3 mask	3.4	96.6	7.5
Face shield	3.8	96.2	16.9
Gloves	4.9	95.1	43.9
Hand sanitation (HCW)	3.2	96.8	29.7
Use of any mask			
HCW	4.0	96.0	72.2
Contact	3.4	96.6	44.6
Combined use of mask			
None	7.9	92.1	22.6
HCW alone	4.8	95.2	32.7
Contact alone	4.2	95.8	5.1
Both HCW and contact	3.2	96.7	39.6
Symptoms (HCW)			
Fever	29.7	70.3	2.3
Cough	15.1	84.9	10.0
Sore throat	4.0	96.0	6.5
Asthenia	13.8	86.2	0.9
Dyspnea	12.1	87.9	1.0
Anosmia/hyposmia	22.9	77.1	0.4
Ageusia/hypogeusia	12.7	87.3	0.5
Migraine	7.6	92.4	1.5
Total	4.9	95.1	100.0

**Effective contacts: contacts followed by a positive PCR test; ineffective contacts: contact not followed by a positive PCR test.*
Note: Of the 2,952 HCWs included, 1,891 (38.7%) reported 1 contact; 1,222 (25.0%) reported 2 contacts; 747 (15.3%) reported three contacts; 436 (8.93%) reported 4 contacts; 195 (4.00%) reported 5 contacts; 322 (6.60%) reported 6-10 contacts; 70 (1.40%) reported >10 contacts.

to use masks compared to men (p=0.056). With reference to job title, administrative staff was less likely to wear masks compared to the other professionals (p<0.001). The OR for hand sanitation was 0.61 (95%CI 0.40-0.93). The use of gloves or of a face shield was not associated with effective contact.

When excluding the first 2 weeks of March, results for the associations between PPE use and risk

Table 3. Odds ratio of infection among HCWs according to sex, age and job title, use of mask, use of other PPEs, symptoms, type of exposure and period of exposure.

Characteristic	OR	95%CI
Sex[1]		
Male	ref	-
Female	0.94	(0.68-1.31)
Age group[2]		
20 - 35	ref	-
36 - 50	1.30	(0.87-1.94)
51 - 70	0.99	(0.65-1.50)
Job title[3]		
Administrative staff / Other	ref	
Physician	1.01	(0.50-2.04)
Resident physician	0.30	(0.11-0.78)
Nurse	0.66	(0.34-1.29)
Health assistant	0.92	(0.44-1.90)
Healthcare professional	0.60	(0.25-1.43)
Use of mask		
Healthcare worker[4]	0.63	(0.45-0.87)
Source[5]	0.63	(0.45-0.89)
Combined use of mask[6]		
None	ref	-
HCW alone	0.59	(0.40-0.86)
Contact alone	0.49	(0.22-1.07)
Both HCW and contact	0.40	(0.27-0.60)
Use of other PPEs[*]		
FFP2 / FFP3[7]	0.48	(0.21-1.09)
Gloves[7]	1.32	(0.85-2.04)
Glasses / Visor[7]	0.82	(0.51-1.31)
Hand sanitization[7]	0.61	(0.40-0.93)
Symptoms[8*]		
Fever	7.25	(3.49-15.08)
Cough	2.75	(1.57-4.84)
Sore throat	0.79	(0.32-1.95)
Asthenia	4.25	(1.38-13.08)
Dyspnea	1.54	(0.48-4.91)
Hyposmia / Anosmia	3.69	(0.32-41.80)
Hypogeusia / Ageusia	0.70	(0.05-9.17)
Migraine	1.15	(0.28-4.65)
Period of exposure[9]		
01.03.2020 - 15.03.2020	ref	-
16.03.2020 - 30.03.2020	0.35	(0.25-0.52)
01.04.2020 - 15.04.2020	0.13	(0.07-0.24)
16.04.2020 - 30.04.2020	0.16	(0.08-0.31)
after 01.05.2020	0.07	(0.02-0.17)
Type of exposure[10]		
Meals, meetings	ref	-
Patient assistance and handling, patient hygiene	1.52	(0.90-2.56)
Medical examination, therapy administration, parameters measurement	0.81	(0.41-1.59)
Room sharing	1.30	(0.76-2.23)
Aerosol generating manipulations, surgery, invasive procedures	0.41	(0.11-1.55)

Notes: OR, odds ratio; CI, Confidence Interval; ref, reference category.
[1]OR adjusted for age group.
[2]OR adjusted for sex. [3]OR adjusted for sex and age group.
[4]OR adjusted for sex, age group, job title and use of mask by source.
[5]OR adjusted for sex, age group, job title and use of mask by HCW.
[6]OR adjusted for sex, age group and job title.
[7]OR adjusted for sex, age group, job title, use of mask, use of other PPEs.
[8]All the ORs are adjusted for sex, age group and other symptoms.
[9]OR adjusted for sex, age group, job title and use of mask.
[10]OR adjusted for sex, age group, period of exposure.
**OR of use of each PPE (reference category: no use of that PPE).*
***OR of presence of each symptom (reference category: absence of that symptom).*

of infection were weaker, with only hand sanitation remaining significantly protective.

ORs for reported fever, cough, asthenia, anosmia/hyposmia, dyspnea, and migraine were all elevated, although the association was not significant for the last three symptoms.

In terms of period and type of exposure, the first half of March 2020 was the period with the highest risk of infection. We found no association between the reported type of exposure and infection. Finally, employment in a COVID-19 designated department was not associated with the risk of infection.

In order to address possible bias from the fact that unprotected contacts might preferentially lead to a test, we repeated the analysis restricted to 579 HCWs who were tested because they reported symptoms. The OR of positive PCR result for use of a mask by both the HCW and the contact compared to use by neither was 0.69 (95%CI 0.34-1.43).

4. Discussion

We reported findings from more than 4,800 detailed COVID-19 contact-reporting forms compiled by over 2,900 HCWs and collected in one of the largest hospitals in Italy. Our analysis suggests that proper mask use (both by the contact and the source of infection) is highly effective for reducing transmission of SARS-CoV-2, with an increasing degree of protection from no use, use by one between HCW or source of infection, and use by both. This latter corresponds to an OR of 0.40 (95%CI=0.27-0.60) for infection compared to no use of a mask.

Evidence that an appropriate PPE use is highly effective in preventing infection among HCWs is well established [10-13]. However, despite several studies supporting their role in controlling SARS-CoV-2 transmission, potential sources of bias commonly affect analyses on PPE use, including misclassification of mask use as well as heterogeneous COVID-19 testing. Also, several previous studies were based on convenience sampling, resulting in possible selection bias [10, 11].

A unique aspect of our study was the ability to integrate information on exposure characteristics and symptoms across multiple potentially effective contacts. This approach increased the chances to match the result of each PCR test with information on the relevant circumstances of exposure to SARS-CoV-2. Our analysis provides useful insight to better understand the prevalence and the spreading of infection in the hospital setting. Weighting each PCR test by the number of potentially effective contacts for which it was prescribed increased the validity of the analysis by avoiding overcounting potentially effective contacts, as well as the arbitrary selection of one of the contacts. This reduced the opportunity for bias in the analysis and represented an improvement over previous analyses on SARS-CoV-2 infections among HCWs, including those done by our group [4].

A key point during contact tracing was risk assessment [14]. Contacts, if not PPE fully protected, entailing prolonged (>15 minutes) sharing of a room, short distance and talking activity, or medical procedures directly on the body and face of a positive subject were considered at risk, and consequently investigated through PCR testing. Among the risk criteria, the correct use of PPE, in which mask was the principal discriminant between appropriate or inappropriate protection, was of importance.

When the strategies to address the pandemic took shape, an increasing number of tests was implemented in the hospital setting [15]. This could have led to the over-testing of HCWs compared to the general population. Anyway, the database analyzed included tests performed based on risk assessment derived from contact tracing, thus the high proportion of HCWs with multiple testing in our study population can be mainly explained by either repeated contacts or by the request of two negative tests for return to work. To enhance both the specificity and the sensitivity of our analysis, we considered all possible contacts – after weighting them – to identify the profile of risk of infection.

Results on mask effectiveness in preventing SARS-CoV-2 infections are not fully consistent between studies among general population and HCWs, with the first group showing lower protective ability than the second one [2]. This can be explained by several factors, including differences in age range, health status, and types and characteristics of PPEs. In fact, community- and hospital-based studies can contribute complementary evidence on the effectiveness of PPE use in preventing SARS-CoV-2 infection, with the latter being particularly accurate in assessing the effectiveness of PPEs in well-controlled circumstances of use by trained individuals. Regarding the use of FFP2/3 masks, we confirmed previous findings about their high effectiveness in preventing-SARS-CoV-2 infection [10, 14].

In our study, wearing gloves was associated with an increased risk of infection while the opposite effect was shown for hand sanitization. While the use of gloves avoids pathogen dissemination, it may provide a false sense of security and may increase virus spread [16], and published studies have led to contradictory results [1]. HCWs should therefore be informed that gloves do not provide complete protection against hand contamination: exposure to pathogens may occur because of defects in gloves or more commonly during glove removal, leading to self-contamination [17]. The recommendation to wear gloves during an entire episode of care of a patient undergoing isolation precautions could actually lead to HCWs missing hand hygiene. This supports the importance of HCWs' training in the sequence of procedures, limiting the use of gloves, and maximizing non-touch techniques during patients' care.

Among this study population gender and age were not associated with the risk of infection. In literature, those findings often disagree [4]. While a sex disparity of COVID-19-related morbidity and mortality have been observed in several studies, with 50% more hospitalized men than women based on data from 6 different European countries-Italy included, no significant difference emerges for SARS-CoV-2 transmission [18]. Also, in a study conducted on HCWs from Veneto, Northern Italy, no difference in SARS-CoV2 antibodies seroprevalence was detected by gender [19]. While an excess risk of infection has been described in men older than 60 [18], our population includes mainly individuals below that age.

We described different risks of effective contact and the prevalence of PPE use in the different health care professionals, including the administrative staff. The timeframe considered in our analysis (March-September 2020) corresponds to the very first wave of the pandemic when the management of daily hospital activities was particularly delicate and went through a progressive reconfiguration. Indeed, in order to limit overcrowding in the hospital, many professionals were assigned to smart working. This not only regarded administrative staff, but also several physicians and nurses (e.g., from department of neurology and surgery). The administrative staff who worked in presence in Turin hospital were assigned to activities of patient acceptance, secretary and back-office. They were provided with hand sanitation gel, surgical masks (or FFP2/3) and protective barriers, with the recommendation to strictly follow social distancing rules. Our analysis showed that administrative staff were less likely to wear mask, while they were not more likely to get infection.

Garzaro et al. carried out a survey based on the first 3,000 contact forms from our center [8] and reported that administrative staff was at higher risk of infection while physicians were the main source of infection. A large review found that nurses were the most commonly infected group of HCWs, despite no evidence of a higher infection rate for those involved in high-risk tasks [20]. These data suggest that factors other than direct contact with infected persons are involved, underlying the role played by PPEs and sanitation, which have been introduced very soon in COVID-19-designated departments for HCWs' protection.

The lack of statistical significance in the sub-analysis excluding the first 2 weeks of March are mainly due to the high prevalence of use of PPE after the very first weeks of Sars-CoV-2 pandemic, while in early March the paucity of PPE use led to the evidence of the differences made by PPE between effective and ineffective contacts.

Our study showed that all HCWs were at comparable risk of infection, with the minor exception of resident physicians. This could be explained by the increased use of PPEs over time. As suggested by Boffetta et al. in a previous study also including a subset of the current population [4], the lack of a job-related pattern of risk indicates that all HCWs share similar risk levels of infection, including those who worked in COVID-19 departments. Further confirmation comes from our results on the type of exposure, which did not identify differences among HCWs reporting high-risk procedures like those generating aerosol compared to common situations like sharing a room or attending a meeting in presence of a positive case. However, this aspect can suffer from reporting bias, since HCWs may have been prone to declare that one of the parties did not correctly wear a mask, because of excessive caution and willingness to be screened. This bias is likely to be non-differential with respect to infection since it was collected before the HCWs knew about their status.

The findings of an early survey conducted among some of the subjects included in this study led to the inclusion of hyposmia/anosmia as major symptoms in the COVID-19 reporting form; this extended analysis further confirms this finding [8]. In addition, accordingly to our risk-assessment protocol, as well as with the literature [21], we found strong associations between infection and fever, cough, and asthenia.

Our study showed a higher risk between 1 March and 15 March, 2020. These data reflect the pandemic situation of that time, when in addition to the novelty of the situation, Italy suffered from a scarcity of PPEs, lack of scientific knowledge, and reduced attention to between-person distancing, enhancing the likelihood of infection transmission both inside and outside the hospital setting. This agrees with the results reported by Wang et al. at the time of the first wave of the pandemic and following the introduction of restrictions and PPE use [13]. In addition, these findings may be associated also with the hospital setting of this study, as SARS-CoV-2 infection heavily affected Italy's healthcare system in the very first phase of the pandemic.

One of the main strengths of this study is the availability of detailed information, particularly on PPE use, including data on the use of facial masks by the source of infection at the time of the contact. These data allowed a quantitative assessment of the effectiveness of wearing surgical mask to prevent SARS-CoV-2 infection. The systematic collection of this information during contact tracing provided the early identification of the typical symptoms of COVID-19 such as hyposmia/anosmia and hypogeusia/ageusia. An additional strength is the large number of HCWs included in the study and the detailed contact-tracing forms based on a standardized procedure. High compliance was demonstrated by HCWs, who fully adhered to the monitoring system set up in the hospital. This is an advantage compared to population-based surveys, in which many people may not be contacted or declined to cooperate [22, 23]. Moreover, multiple tests in the same subject were based on the same assay, enabling a valid comparison of the results. Finally, we were able to identify a set of contacts likely to include the one responsible for the infection. This allowed us to combine the use of masks by the HCW and the case index and to analyze different exposure circumstances, where none using a mask identified the highest likelihood of SARS-CoV-2 transmission and both using a mask the lowest. Given the personal concern of HCWs for their own health as well as that of their patients and families, and the lack of negative consequences in case of incorrect use of PPEs, it is likely that mask reporting was more sensitive than specific. This misclassification was likely non-differential with respect to the infection status, leading to an underestimate of the effectiveness of surgical masks. The reliability of this information is likely to be good because the forms were used as part of a standardized contact tracing procedure and most of them were completed within 10 days from the contact.

This study suffers from some limitations. First, we did not have information on SARS-CoV-2 variants, as our data refer to the first phase of the epidemic. In addition, we did not consider super-spreading events, and we could only partially characterize the type of exposure to infection, as the information on extra-occupational exposure circumstances was self-reported and was not based on a standardized questionnaire. Furthermore, we could not investigate the difference between sources of infections (i.e., patients, colleagues, relatives, or friends). Similarly, the information on symptoms was self-reported and therefore subject to some degree of misclassification, which, as in the case of PPE use discussed above, was likely to be non-differential. Finally, we did not have information on chronic conditions of HCWs, which might have increased the risk of SARS-CoV-2 infection, although it is not certain that these conditions would be associated with a higher probability of an effective contact, thus exerting a confounding effect.

The unit of the statistical analysis was the contact. During the timeframe considered, the same HCW could have notified to Occupational Medicine Unit several contacts. Moreover, multiple contacts could have been reported by the same HCW in a very short time, because of the spreading of outbreaks of infection in the hospital, leading to one single PCR test. For these reasons, the number of subjects reporting contacts does not correspond to the number of tests. This does not apply only to this specific population but reflectshe circumstances of COVID-19 pandemic, and particularly its first wave.

We tried to address this problem by focusing on the number of contacts, which was an intermediate measure among subjects and PCR tests performed, and because our aim was to determine which factors were associated to effective contacts, namely notified contacts which ended up with COVID-19 transmission assessed by PCR test. The limitation of this approach is that when the same subject declared different contacts, the personal characteristics of the subject were taken into account multiple times (namely, sex, age, and job title), which we addressed by includinh weights. Conversely, the different contacts by the same subject may differ according to use of PPE, type of contacts and other characteristics independent from the subject.

The results obtained are useful to clarify the predictors of SARS-CoV-2 transmission, whose understanding is of primary interest to reduce the likelihood of infection even in the global vaccination era and for emergency phases of future pandemics. Characterization of risk based on mask use helps in the risk assessment and corroborates the fact that mask use must be required in the hospital setting to guarantee the safety of both HCWs and patients. Indeed, PPEs remain a fundamental set of tools even among vaccinated, thus their correct use should be encouraged. This is especially important in worksites at high exposure to public, where contact with unvaccinated or even positive subjects, whether symptomatic or not, is frequent. The study is based on data collected during the first phase of the pandemic, when knowledge about virus spreading was limited and hospitals had to deal with an increasing number of potentially infected patients, that challenged both the clinical infrastructure and the occupational surveillance. Further studies on the combined use of PPEs analyzed with respect to different hypothetical conditions of SARS-CoV-2 transmission are worthwhile. Models on the potential public health interventions which should have been successful in avoiding the pandemic, and the prompt recommendation of using surgical masks, would be of high value for the future. It should also be considered that the frequency of SARS-CoV-2 infection is dependent on the geographical exposure to the virus and primarily to family rather than hospital exposure [24].

5. Conclusions

This study provided evidence of masks' protective effect during SARS-CoV-2 exposure. The study refers to the first pandemic wave when the virus spreading knowledge was limited and hospitals had to deal with increased number of patients without renouncing security procedures. PPEs shortage was an issue worldwide and many questions on their suitability were risen, in particular, whether surgical masks could provide an adequate standard of protection compared to FFP2/3 masks. This study demonstrates that surgical masks (especially if worn by both the HCW and the contact) offer a similar protection compared to FFP2/3.

Institutional review board statement: The study was approved by the Institutional Review Board of the University Hospital of Turin. The Review Board waived the request for informed consent from study participants. All methods were performed in accordance with the relevant guidelines and regulations.

Declaration of interest: The authors declare no conflict of interest.

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References

1. Chou R, Dana T, Buckley DI, Selph S, Fu R, Totten AM. Epidemiology of and Risk Factors for Coronavirus Infection in Health Care Workers: A Living Rapid Review. *Ann Intern Med*. 2020;173:120-36.
2. Chu DK, Akl EA, Duda S, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and

COVID-19: a systematic review and meta-analysis. *Lancet*. 2020;395:1973-87.
3. Tabah A, Ramanan M, Laupland KB, et al. Personal protective equipment and intensive care unit healthcare worker safety in the COVID-19 era (PPE-SAFE): An international survey. *J Crit Care*. 2020;59:70-5.
4. Boffetta P, Violante F, Durando P, et al. Determinants of SARS-CoV-2 infection in Italian healthcare workers: a multicenter study. *Sci Rep*. 2021;11:5788.
5. Luo L, Liu D, Liao X, et al. Contact Settings and Risk for Transmission in 3410 Close Contacts of Patients With COVID-19 in Guangzhou, China: A Prospective Cohort Study. *Ann Intern Med*. 2020;173:879-87.
6. Cheng HY, Jian SW, Liu DP, et al. Contact Tracing Assessment of COVID-19 Transmission Dynamics in Taiwan and Risk at Different Exposure Periods Before and After Symptom Onset. *JAMA Intern Med*. 2020;180:1156-63.
7. Trémeaux P, Lhomme S, Abravanel F, et al. Evaluation of the Aptima™ transcription-mediated amplification assay (Hologic®) for detecting SARS-CoV-2 in clinical specimens. *J Clin Virol*. 2020;129:104541.
8. Garzaro G, Clari M, Ciocan C, et al. COVID-19 infection and diffusion among the healthcare workforce in a large university-hospital in northwest Italy. *Med Lav*. 2020;111:184-94.
9. StataCorp. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC, 2019.
10. Rader B, White LF, Burns MR, et al. Mask-wearing and control of SARS-CoV-2 transmission in the USA: a cross-sectional study. *Lancet Digit Health*. 2021;3:e148-57.
11. Tabatabaeizadeh SA. Airborne transmission of COVID-19 and the role of face mask to prevent it: a systematic review and meta-analysis. *Eur J Med Res*. 2021;26:1.
12. Talic S, Shah S, Wild H, et al. Effectiveness of public health measures in reducing the incidence of covid-19, SARS-CoV-2 transmission, and covid-19 mortality: systematic review and meta-analysis. *BMJ*. 2021;375:e068302.
13. Wang X, Ferro EG, Zhou G, Hashimoto D, Bhatt DL. Association Between Universal Masking in a Health Care System and SARS-CoV-2 Positivity Among Health Care Workers. *JAMA*. 2020;324:703-04.
14. Wang Y, Deng Z, Shi D. How effective is a mask in preventing COVID-19 infection? *Med Devices Sens*. 2021:e10163.
15. Romagnani P, Gnone G, Guzzi F, et al. The COVID-19 infection: lessons from the Italian experience. *J Public Health Policy*. 2020;41:238-44.
16. European Center for Disease Prevention and Control. Technical Report. Use of gloves in healthcare and non-healthcare settings in the context of the COVID-19 pandemic. Solna, Sweden: ECDC, 2020. https://www.ecdc.europa.eu/en/publications-data/gloves-healthcare-and-non-healthcare-settings-covid-19.
17. WHO Guidelines on Hand Hygiene in Health Cancer (Advanced Draft). Geneva, Switzerland: World Alliance for Patient Safety,WHO, 2006. www.who.int/gpsc/en/index.html.
18. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. *Biol Sex Differ*. 2020;11:29.
19. Plebani M, Padoan A, Fedeli U, et al. SARS-CoV-2 serosurvey in health care workers of the Veneto Region. *Clin Chem Lab Med*. 2020;58:2107-11.
20. Gómez-Ochoa SA, Franco OH, Rojas LZ, et al. COVID-19 in Health-Care Workers: A Living Systematic Review and Meta-Analysis of Prevalence, Risk Factors, Clinical Characteristics, and Outcomes. *Am J Epidemiol*. 2021;190:161-75.
21. European Center for Disease Prevention and Control. Clinical characteristics of COVID-19. Solna, Sweden: ECDC, 2021. https://www.ecdc.europa.eu/en/covid-19/latest-evidence/clinical
22. Stringhini S, Wisniak A, Piumatti G, et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. *Lancet*. 2020;396:313-9.
23. Poustchi H, Darvishian M, Mohammadi Z, et al. SARS-CoV-2 antibody seroprevalence in the general population and high-risk occupational groups across 18 cities in Iran: a population-based cross-sectional study. *Lancet Infect Dis*. 2021;21:473-481.
24. Sandri MT, Azzolini E, Torri V, et al. SARS-CoV-2 serology in 4000 health care and administrative staff across seven sites in Lombardy, Italy. *Sci Rep*. 2021 Jun 10;11(1):12312. Doi: 10.1038/s41598-021-91773-4. PMID: 34112899; PMCID: PMC8192543.

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A method for the risk assessment of biomechanical overload in hospital physiotherapists

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Keywords: Functional rehabilitation technicians; work-related musculoskeletal disorders; dysergonomies; health surveillance

Abstract

Background: *In physiotherapists, biomechanical overload risk assessment (RA) is particularly complex due to the tasks' variability. The present study aims to propose a new methodology, named Whole Body RA Musculoskeletal Biomechanical Overload (WB-RAMBO), to assess the risk in the activities performed by physiotherapists.* **Methods:** *Each type of intervention was broken down into elementary operations. The risk factors (force, repetitiveness, and incongruous postures) were recorded and evaluated for each of these. For each task, the risk level was obtained by integrating the results of multiple ergonomic methods among those proposed by the international literature. To verify and validate the obtained results, we reviewed the medical records of health surveillance carried out on physiotherapists.* **Results:** *From the ergonomic point of view, RA shows a situation of acceptability. The observed slight dysergonomies are diluted in the work shift and allow an optimal functional recovery of the musculoskeletal system.* **Conclusions:** *This method proposes a RA for each operation performed. A work plan subjected to such a peculiar RA can be redesigned and adapted to the company's and the hypersusceptible worker's organizational needs.*

1. Introduction

Numerous literature studies show that functional rehabilitation technicians [1-6], more commonly known as physiotherapists, are potentially exposed to the risk of biomechanical overload to the musculoskeletal system. RA from biomechanical overload to which these operators are exposed is particularly complex due to the extreme variability of the tasks. The related overload depends not only on organizational and structural aspects but also mainly on the level of impairment and the residual functional ability of the patient, so it is difficult to propose a standardized methodology for RA.

Many methods proposed in the international literature (e.g., REBA [7], HAL ACGIH [8], OCRA [9], STRAIN INDEX [10]) assess single risk factors or body segments. MAPO (Assisted Handling of Hospitalized Patients) is another method extensively used in health care (HC) facilities

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[11, 12], but its primary outcome is not focused on RA but on risk management by organizational and structural preventive measures. The HOARA (Holistic Approach RA method) [13] can allow the RA for head/neck, spine, and upper and lower limbs resulting from activities performed by health care workers (HCWs) in the work shift. HOARA is a new tool developed for both RA and risk management.

Our study was carried out with the primary objective of developing an innovative methodology, named Whole Body RA Muskuloskeletal Biomechanical Overload (WB-RAMBO), to assess the risk of biomechanical overload to the musculoskeletal system in the activities performed in outpatient clinics and inpatient wards by physiotherapists employed in a large university hospital.

2. Methods

The study was carried out at the Spedali Civili Hospital of Brescia, Brescia, Italy, with the support of the Coordinator of the Physiotherapy Unit, who provided accurate information about the type, frequency, and duration of the different rehabilitation interventions (tasks) carried out by physiotherapists both in the inpatient wards and the outpatient clinic (Table 1).

For the interventions carried out on the wards, since these are difficult to standardize, as they are strictly dependent on the level of impairment of the inpatients, the work plans and activity diaries for all the interventions carried out by each physiotherapist for a month were analyzed.

The outpatient interventions are, on the contrary, more standardized; we evaluated all the types of intervention carried out by the physiotherapist in the outpatient clinic, defining each of their frequency and duration in the work shift.

Each intervention was broken down into elementary operations, recording every dysergonomy regarding force commitment, repetitive movements, and maintenance of incongruous postures. The duration of each observed dysergonomy was summed, resulting in the overall biomechanical overload per work shift as a basis for RA by the multi-method methodology.

Such work was followed by direct observation and video filming of some rehabilitation interventions both on the wards and in outpatient clinics.

Each physiotherapist was observed for a half-shift during ward activity, as videotaping patients was impossible. The interventions carried out on seven patients (out of the 14 assigned to a single physiotherapist per shift) in the departments of Orthopedics and Traumatology, Internal Medicine, and Neurology were evaluated. The times of incongruous posture of the various articular districts of the upper limb (shoulder, elbow, wrist-hand), spine, and lower limbs and the number and duration of actions in force for each operation performed during the intervention on each patient were recorded.

Regarding the outpatient interventions, the activities of physiotherapists with more seniority in the department were videotaped, showing the rehabilitation interventions carried out on colleagues who acted as actors, with subsequent ergonomic evaluation.

For each task, the risk was calculated by integrating the results of multiple assessment methods from those proposed by the international literature.

As in our previous contributions [14-17], the RA followed the methodology indicated in the SIML Guidelines [18] on work-related musculoskeletal disorders and pathologies and according to the technical standard ISO 11228-3 [19]. The preliminary assessment consisted of verifying the existence of specific "items" proposed by the Washington State Assessment Standard (Caution Zone Checklist Washington, CZCW) [20]. The Standard's more complex analytical level checklist (Hazard Zone Checklist Washington, HZCW) was applied to all investigated operations [20]. We chose this RA method because it guarantees the possibility of performing a holistic assessment of the biomechanical overload for the entire musculoskeletal system: spine, upper and lower limbs. The posture was assessed according to the technical standard ISO 11226:2000 [21]. This standard allows the analysis of static postures of the spine necessary for rehabilitation activities performed by physiotherapists.

For the assessment of manual handling tasks in lifting and pulling-pushing, the NIOSH equation for calculating the compound lifting index (ISC) [22] and the Snook and Ciriello tables [23] were used, respectively. The ACGIH-HAL methods [8] and the Italian version of the OREGE method

Table 1. Operations for rehabilitation purposes performed in inpatient wards. A: Orthopaedic patient (simple or multiple trauma); B: Multi-pathologic/Complex patients; C: Neurological/Neurosurgical patients; D: Critical Care Area patients; E: Outpatient clinic.

Operations	**A**	**B**	**C**	**D**	**E**
Patient identification, consultation, and review of medical records (in particular to rule out relative or absolute contraindications to treatment) by ward staff	x	x	x	x	x
Assessment of the patient's condition and vital signs				x	x
Evaluation and adjustment of the rehabilitation setting in which to carry out the treatment (evaluating and adjusting the presence of a catheter, nasogastric tube, or other devices and monitoring systems)	x	x	x	x	x
Positioning the patient in a correct posture	x	x	x	x	x
Passive or active-assisted mobilization at the bedside of the affected body district (usually mobilization of at least three joint districts bilaterally)	x	x	x	-	x
Passive or active-assisted bedside mobilization of upper and lower limbs and, if possible, of the neck and head (approximately 10 to 20 repetitions for all joint areas)				x	x
Sensory-motor stimulation and reactivation of the affected body districts			x	x	x
Active mobilization and muscle strengthening of the affected area (usually reactivation of at least three joint areas bilaterally)	x	x / with breathing exercises	x		x
Reaching and maintaining a sitting position (with the possible simultaneous addition of exercises to realign the trunk muscles)	x	x	x		x
Reaching and maintaining a sitting position (with exercises for reaching and maintaining the midline, axial loading, and reactivation of the trunk)			x	x / at least two physiotrp	x
Achieving and maintaining a standing position	x	x / help of 1-2 physiotrp	x / help of 1-2 physiotrp		x
Walking with help or supervision of a physiotherapist (with or without aid)	x	x	x		x
Wheelchair with correct postural alignment in bed or chair and orthotic positioning	x	x	x	x	x

developed by the French INRS [24, 25] were used to assess the risk of biomechanical overload of the upper limb. Among the various methods proposed in the international literature, the manual activity index offers the possibility of having an estimate of the risk focused on the hand-wrist district, which is mainly involved in some peculiar rehabilitation activities such as manipulations and bandages. The OREGE method thoroughly evaluates all anatomical districts of the upper limb and cervical spine.

Figure 1 shows the step-by-step evaluation phases to explain better and visualize the calculations performed to define the risk.

To verify/validate the risk assessment, we retrieved the results of the health surveillance carried out according to Italian Legislative Decree 81/08 over the last five years, aggregating them according to the occurrence of musculoskeletal pathologies and stratifying them by gender and age. Overall, we evaluated 221 medical records of 160 workers and calculated

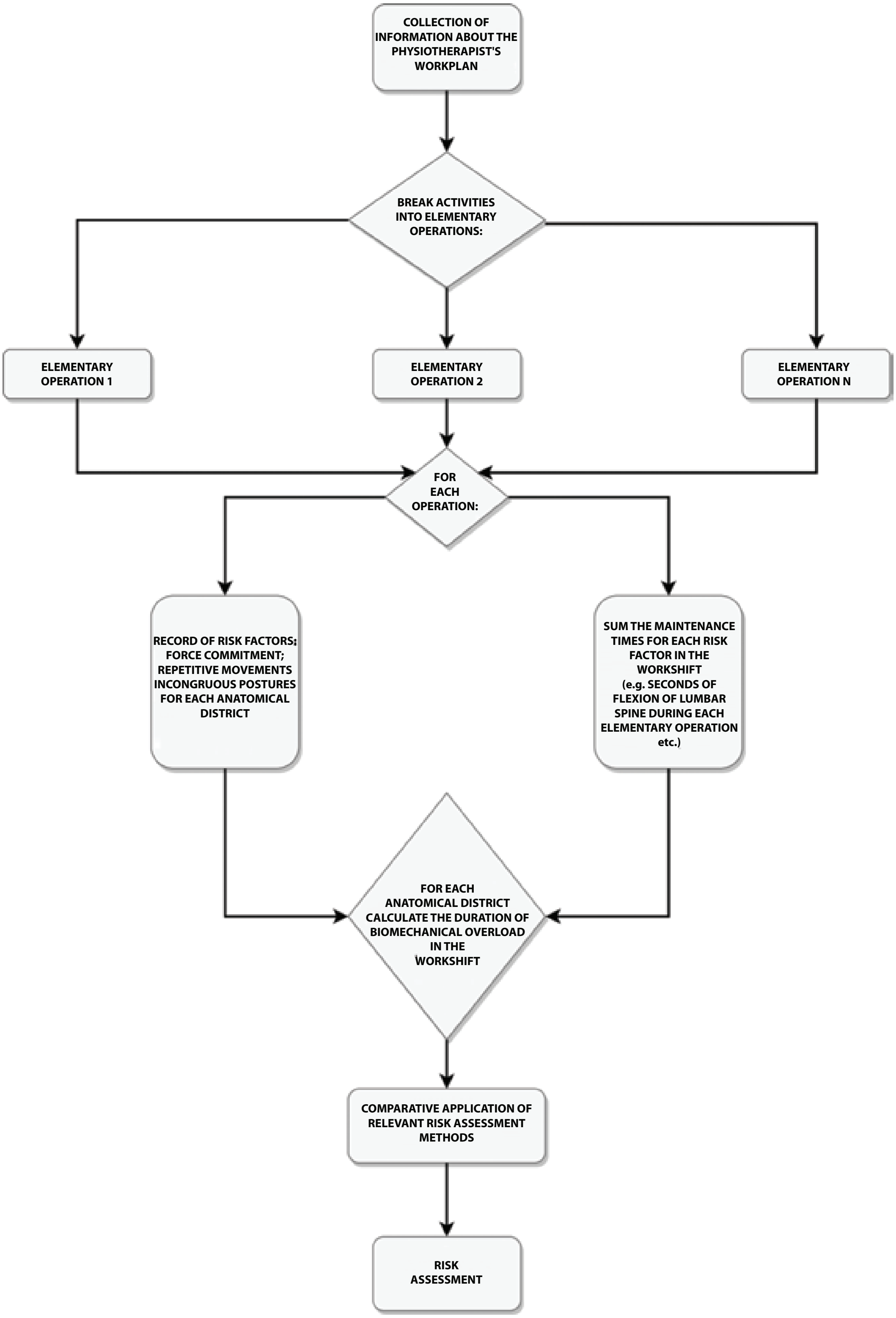

Figure 1. Diagram of the calculation performed to define the risk.

the incidence and prevalence of musculoskeletal diseases and disorders during the considered period.

3. Results

The information obtained by the coordinators by breaking down the work plans into tasks (rehabilitation interventions) and elementary operations resulted in the sequences of activities highlighted in Table 1 for interventions in the wards.

Table 2 shows the results of the RA for the different rehabilitation interventions. Only for the activities in Orthopedics and Medicine departments (Comprehensive Rehabilitation), the preliminary risk assessments, according to Caution Zone Checklist of State of Washington (CZCW) [20], showed the need for in-depth assessment of the risk of manual handling of patients with methods of higher analytical level such as the Hazard Zone Checklist of State of Washington (HZCSW) [20], as well as the assessment according to the technical standard ISO 11226:2000 [21] that did not show critical issues worthy of note.

For all the other workstations investigated, there were no critical points relating to the manual handling of loads. The dysergonomies observed at the upper limb, spine, and knee level are noted in Table 3, with an indication of their duration and entity. In any case, these do not configure a significant risk. They are diluted in the work shift, allowing an optimal functional recovery of the musculoskeletal system. However, a few suggestions for preventive interventions are presented at the end of the same table.

The pooled results of the health surveillance carried out in 2016-2021 show 21 physiotherapists out of 160 (13%) affected by at least one musculoskeletal pathology and five (3%) by more than one. Table 4 shows the main characteristics of the analyzed population.

The 26 musculoskeletal pathologies found are distributed as follows: 12 (46%) cervical discopathies, 7 (27%) shoulder tendinopathies, 3 (11%) coxarthrosis, 1 (4%) spondylolisthesis, 1 (4%) rhizarthrosis, 1 (4%) dorsal discopathy and 1 (4%) lumbosacral discopathy (Figure 2).

The diagnosis of these pathologies was always supported by the reports of instrumental examinations such as muscle-tendon ultrasound and magnetic resonance imaging (MRI) for shoulder and radiography (RX) and MRI for lumbosacral discopathy. The pathologies' onset is before the period considered, the most recent one dating back to 2010. None of the pathologies presents characteristics of technopathy. Local trauma and subacromial impingement played a significant role in the onset of the tendinopathies observed in 7 of the 8 musculoskeletal pathologies analyzed. The only case of lumbosacral discopathy was recognized as an occupational disease for other work performed before employment in the physiotherapy department before 2016.

4. Discussion

Although numerous literature studies have investigated biomechanical risk factors for functional rehabilitation technicians [1-3, 26-29], there are relatively few studies assessing the magnitude of these risks and comparing the results of RA with the prevalence of musculoskeletal disorders in employees diagnosed by imaging techniques. Studies using surface electromyography (sEMG) combined with questionnaires have been conducted to assess the risk of biomechanical overload of the upper limb in physiotherapists [4]; sEMG combined with 3D camera recording and load cells has been exploited experimentally to quantify biomechanical overload of the spine and lower limb during manual mobilization of patients [30]. The European report (Assessing Arm Elevation at Work with Technical Systems, PEROSH Joint Research Project Recommendations for procedures to measure occupational, physical activity and workload, 2018) [31] recommends instrumental and observational RA methods a best practice, especially where the observational method can help the interpretation of experimental data.

Aims of future studies will be the objectification of risk analysis performed using observational methods with objective RA tools (surface electromyography, load cells, kinematic sensors, and optoelectronic systems).

Furthermore, the proposed method could be extended to other healthcare workers engaged in

Table 2. Results of the biomechanical overload RA of the spine and upper limb in different rehabilitation interventions.

Department / Intervention	Caution Zone Checklist W	Hazard Zone Checklist W	ISO 11226:2000	NIOSH	Snook - Ciriello	HAL ACGIH	OREGE
Orthopedics and Traumatology[1]	+ MMC > 34 Kg 1 die	0	A				
Medicine (comprehensive rehabilitation)	+ MMC > 34 Kg 1 die	0	A				
Neurosurgery[1]	0	0	A				
Outpatient clinics[1]	0	0	A				
US immersion activities	0	0	A	A ISC M 18-45 yy. : 0,41 M <18 yy. >45 yy. : 0,51 F 18-45 yy. : 0,51 F <18 yrs and >45 yrs 0,68	Low risk I.S.R. F.I. Thrust (M): 0.02 I.S.R. F. M (M):0.02 I.S.R. F.I. Thrust (F): 0.04 I.S.R. F. M (F): 0.03		
US massage activities	0	0	A		Low risk I.S.R. F.I. Thrust (M): 0.19 I.S.R. F. M (M):0.17 I.S.R. F.I. Thrust (F): 0.26 I.S.R. F. M (F): 0.29		
Lower limb adhesive-elastic bandage	0	0	A				A(6)
Lower limb rehabilitation	0	0	A			A	A(6)
Locked shoulder	0	0	A				
Dystrophic patient	0	0	A				
Pediatric clubfoot	0	0	A				
Pediatric Myogenic Torticollis	0	0	A				

Legend: A: acceptable; 0: no item present; ISC: complex lifting index; I.S.R. F.I.: Risk index for the initial force in thrust; I.S.R. F.M.: Risk index for thrust holding force; MMC: manual handling of loads.

Table 3. Duration of dysergonomies observed in the working shift for different musculoskeletal segments.

	Upper limb						Spine		Inf. limb
Interventions	**Side***	**Shoulder**	**Elbow**	**Wrist**	**Force Pinch**	**Force commitment**	**C**	**L**	**Knee**
Orthopedics and Traumatology	R	16'03"	3'02"	15'50"	2'06"	5'55"	22'12"	25'31"	28'9"
	L	12'10"	3'47"	7'41"	4'3"	6'7"			
Medicine (comprehensive re-education)[1]	R	10'05"	-	-	-	6' 7"	22'12"	3'30"	5'
	L	10'05"	-	-	-	6' 7"			
Neurosurgery	R	10"	3'02"	14'	-	3'max/5' moderate	2'	10'	2'
	L	-	-	-	-	-			
Outpatient clinics	R	12"	-	26'30"		62'	12'	29'	-
	L	-	-	-	-	-			
Ultrasound massage	R	-	-	-	-	-	-	4"	-
	L	-	-	-	-	-			
Lower limb adhesive-elastic bandage[2]	R	-	-	10'6"	-	-	-	-	-
	L	-	-	-	-	-			
Lower limb	R	5' nc	-	-	4'10" (minimum force)	-	5' nc	5' nc	-
	L	-	-	5'nc	-	-			-
Locked shoulder	R	-	-	86'35" nc	-	-	25'40" nc	7' nc	-
	L	-	-	-	-	-			-
Dystrophic patient[3]	R	-	-	32'nc	-	-	19'50" nc	10'25" nc	-
	L	-	-	-	-	-			-

Legend: nc: non-continuous.
[1] Squatting for 5' with the first patient is not necessary. It would be appropriate to eliminate this dysergonomy by replacing this posture with sitting on a chair.
[2] Need to keep the bandages taut when applying them to the affected limb. Consequently, it is essential to have a height-adjustable table to avoid elevation of the shoulders or flexion of the cervical spine, or incongruous postures of the lumbar spine.
[3] Fully uncooperative patient, positioned for treatment on two juxtaposed couches. Consequently, to treat a hemisoma, the operator must kneel on the couch to perform the treatment.
**R: Right, L: Left*

Table 4. Characteristics of workers.

Number of physiotherapists	Mean Age (years)	Length of service (years)	Physiotherapists with symptoms	WRMSDs	Not WRMSDs
160	47,5	19,46	21* (13%)	1*°	25*
32 Male 128 Female			0 (0%) Male 21 (100%) Female		

** More than one MSD affected the same physiotheraphist.*
° Pathology diagnosis before employment in the physiotherapy department.

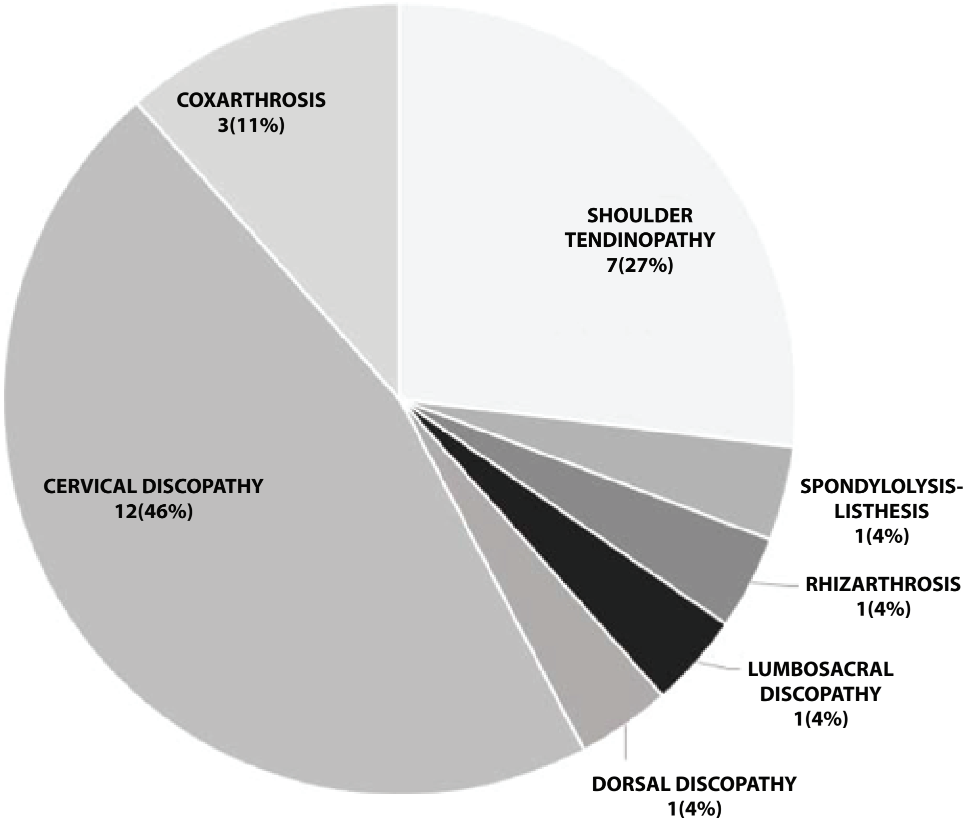

Figure 2. MSDs distribution in physiotherapists from 2016 to 2021.

highly demanding biomechanical tasks in medical and surgical wards.

The main aim of our study was to set up a methodology (WB-RAMBO) for a holistic RA of biomechanical overload to all musculoskeletal segments, including upper and lower limbs and spine for all the activities performed by physiotherapists during the work shift, according to information drawn from work plans and activity diaries.

As already extensively described in the "Methods" section of this contribution, the choice of the methods used to carry out the RA was directed towards methods allowing the analysis of the entire musculoskeletal apparatus (upper limbs, lower limbs, and spine). We also chose methods that allowed a deepening of the biomechanical overload for certain anatomical districts considered more stressed in this activity. Since the starting basis of WB-RAMBO is the operators' work plan, the multi-methodological comparative approach proposed here may, in the future, be modified by choice of other methods more focused on the analysis of the districts most overloaded by the performed tasks. However, the objective of WB-RAMBO remains the multi-methodological RA of the tasks identified in the work plans of healthcare workers (HCWs) employed in outpatient and ward activities.

With the WB-RAMBO method, we performed a biomechanical overload RA for all tasks carried out by rehabilitation technicians based on field observation and videotaping of both outpatient and inpatient activities. As previously highlighted, the daily activities performed by physiotherapists cannot be standardized due to the variability of the patients treated. We tried to overcome such bias by following the same operator in a half-day or an entire 8-hour shift to represent the workload better. Where not possible, activities were simulated by experienced staff. The diaries of the activities carried out in a month of work were also examined to verify whether the observed shift could be defined as "standard" and, therefore, whether all the types of rehabilitation intervention carried out had been subject to evaluation.

The results of our RA method show a situation of acceptability from the ergonomic point of view, both for outpatient and ward activities. The comparative multi-methodological analysis has shown the absence of significant dysergonomies in terms of extent and duration in the shift. The observed ones, although of slight entity, are diluted in the work shift and allow an optimal functional recovery of the musculoskeletal apparatus.

The results were compared with the evidence from worker health surveillance to verify their accuracy. In this specific hospital, such a comparison confirmed RA results with little evidence of physiotherapists' musculoskeletal pathologies (Figure 1). Although with wide variability in prevalence among the different data available in the literature, physiotherapists have the highest prevalence of musculoskeletal disorders in the lumbar spine district (32-80% of reported disorders) [1, 2, 26, 32-34]. In the analyzed sample, the highest percentages are found for cervical discopathy (46%).

A prevalence of 27% emerges for shoulder tendinopathy. Such a prevalence is consistent with only some literature data [33, 34], whereas lumbosacral discopathies account for only 4%, values lower than those reported in the literature for this district [1, 2, 26, 32-34].

5. Conclusions

In conclusion, our study demonstrates that the evaluated physiotherapist tasks can be considered "safe" from an ergonomic point of view. There are no dysergonomies of such duration and entity as to configure an overload for the musculoskeletal system of workers.

The analysis of health data confirms the results of the risk assessment, the prevalence of MSDs is, in fact, lower in our population than in the literature data. WB-RAMBO method allows us to sound out the work plans and analyze each elementary task in biomechanical overload, which is particularly useful for defining prevention measures and better managing the fitness of hypersusceptible workers. The point is particularly useful for occupational physicians in managing hypersusceptible workers whose professionalism does not make them easily relocatable to other operating units. Such subjects can be adequately protected, excluding them from most overloading sub-tasks while maintaining the rest of other activities. Weighing up the duration and frequency of each sub-task makes it easier to draw up a personalized work plan for a worker suffering from a musculoskeletal disease or disorder.

From the management point of view, such a detailed analysis of the work plan allows for intervention by reorganizing the plan itself, where necessary, through a congruous distribution among workers and in the shift of sub-tasks with a more significant biomechanical load. This tool is handy to the Coordinator in drawing up the work plan because it is thus able to distribute the operations with more significant overload better and alternate them with a less biomechanical load. Our study proposes a holistic assessment of biomechanical overload to the musculoskeletal apparatus for each activity performed by the physical therapist through a multimethodological assessment approach with few precedents in the literature [13]. The starting point for identifying the activities under evaluation is the physical therapist's work plans and activity diaries. The assessment of risk from biomechanical overload to the musculoskeletal system must be based on official technical-organizational data by providing for the collaboration of all the professional figures involved: occupational physician, company management, coordinators, workers. A work plan subject to such a peculiar analysis can be redesigned and adapted to the organizational needs of the company but also to the hypersusceptible worker to ensure constant worker-environment-work compatibility [35].

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki. Ethical review and approval were waived for this study, as it was performed in the context of risk assessment in the occupational context, that is compulsory according to the Italian Decree 81/2008.

Informed Consent Statement: Patient consent was waived due to the reasons above explained. Data were treated according to the Italian Legislative Decree 196/2003 and the EU Regulation 2016/679.

Declaration of Interest: The authors declare no conflict of interest.

References

1. Rozenfeld V, Ribak J, Danziger J, Tsamir J, Carmeli E. Prevalence, risk factors and preventive strategies in work-related musculoskeletal disorders among Israeli physical therapists. *Physiother Res Int*. 2010;15(3):176-184. Doi:10.1002/pri.440
2. Grooten WJ, Wernstedt P, Campo M. Work-related musculoskeletal disorders in female Swedish physical therapists with more than 15 years of job experience: prevalence and associations with work exposures. *Physiother Theory Pract*. 2011;27(3):213-222. Doi:10.3109/09593985.2010.481323
3. Petracca M, Bongiorni M, Bartoletti R, Villa L, Candura SM. Movimentazione manuale, idoneità alla mansione e disturbi muscolo-scheletrici negli operatori sanitari dell'Ospedale di Sondrio [Manual handling, job fitness, and musculoskeletal disorders in the Sondrio hospital (Italy) healthcare workers.]. *G Ital Med Lav Ergon*. 2018;40(4):203-207.
4. Lupi A, Martinelli R, Tobia L, Paoletti A. Valutazione del rischio da sovraccarico biomeccanico dell'art superiore nei tecnici di fisiokinesiterapia [Evaluation of risks of biomechanical overload of the upper limb in physical kinesis therapists]. *G Ital Med Lav Ergon*. 2005;27(2):235-236.
5. Gerbaudo L, Violante B. Correlazione tra disturbi muscolo-scheletrici e posture disergonomiche in un gruppo di operatori sanitari di un'azienda ospedaliera [Relationship between musculoskeletal disorders and work-related awkward postures among a group of health care workers in a hospital]. *Med Lav*. 2008;99(1):29-39.
6. Passier L, McPhail S. Work related musculoskeletal disorders amongst therapists in physically demanding roles: qualitative analysis of risk factors and strategies for prevention. *BMC Musculoskelet Disord*. 2011;12:24. Published 2011 Jan 25. Doi:10.1186/1471-2474-12-24
7. Hignett S, McAtamney L. Rapid entire body assessment (REBA). *Appl Ergon*. 2000;31(2):201-205. Doi:10.1016/s0003-6870(99)00039-3
8. ACGIH. American Conference of Governmental Industrial Hygienists (ACGIH). TLVs and BEIs. Cincinnati: American Conference of Governmental Industrial Hygienists; 2000.
9. Occhipinti E, Colombini D, Occhipinti M. Metodo Ocra: messa a punto di una nuova procedura per l'analisi di compiti multipli con rotazioni infrequenti [Ocra Method: development of a new procedure for analysis of multiple tasks subject to infrequent rotation]. *Med Lav*. 2008;99(3):234-241.
10. Moore JS, Garg A. The Strain Index: a proposed method to analyze jobs for risk of distal upper extremity disorders. *Am Ind Hyg Assoc J*. 1995;56(5):443-458. Doi:10.1080/15428119591016863
11. Battevi N, Menoni O, Ricci MG, Cairoli S. MAPO index for risk assessment of patient manual handling in hospital wards: a validation study. *Ergonomics*. 2006;49(7):671-687. Doi:10.1080/00140130600581041
12. Menoni O, Ricci MG, Panciera D, Occhipinti E. Valutazione dell'esposizione ad attività di movimentazione manuale dei pazienti nei reparti di degenza: metodi, procedure, indice di esposizione (MAPO) e criteri di classificazione [The assessment of exposure to and the activity of the manual lifting of patients in wards: methods, procedures, the exposure index (MAPO) and classification criteria. Movimientazione e Assistenza Pazienti Ospedalizzati (Lifting and Assistance to Hospitalized Patients)]. *Med Lav*. 1999;90(2):152-172.
13. Baracco A, Coggiola M, Bosio D, et al. Whole body biomechanical burden of healthcare workers: proposal for a complementary risk assessment and management tool (HOARA). *Med Lav*. 2019;110(5):372-388. Published 2019 Oct 29. Doi:10.23749/mdl.v110i5.7624
14. Sala E, Torri D, Apostoli P. Esperienze di applicazione della valutazione del rischio dalle Linee Guida SIMLII sul rischio biomeccanico per l'arto superiore [The risk assessment procedures from SIMLII guidelines on upper extremity musculoskeletal disorders: discussion on results about a casistic from different working conditions]. *G Ital Med Lav Ergon*. 2008;30(3 Suppl):20-25.
15. Sala E, Torri D, Tomasi C, Apostoli P. Stima del rischio da sovraccarico biomeccanico all'arto superiore condotta, con l'impiego di più metodi di analisi, in diversi settori manifatturieri [Risk assessment for upper extremity work related muscoloskeletal disorders in different manufactures by applying six methods of ergonomic analysis]. *G Ital Med Lav Ergon*. 2010;32(2):162-173.
16. Sala E, Bonfiglioli R, Fostinellil J, et al. Metodi di valutazione del rischio da sovraccarico biomeccanico all'apparato muscolo scheletrico a confronto: esperienza applicativa di dieci anni [Risk assessment comparison of biomechanical overloading of the musculoskeletal system: 10 years' applied experience]. *G Ital Med Lav Ergon*. 2014;36(4):260-266.
17. Apostoli P, Sala E, Curti S, Cooke RM, Violante FS, Mattioli S. Loads of housework? Biomechanical

assessments of the upper limbs in women performing common household tasks. *Int Arch Occup Environ Health*. 2012;85(4):421-425. Doi:10.1007/s00420-011-0690-z
18. Apostoli P, Occhipinti M, Romano C, et al. Linee guida per la prevenzione dei disturbi e delle patologie muscolo scheletriche dell'arto superiore correlati con il lavoro. Pavia Pime Editrice 2006.
19. British Standards Institute. BS ISO 11228-3:2007 *Ergonomics* - Manual handling - Part 3: Handling of low loads at high frequency. 2015;3(August). Avaiable on line at: https://www.iso.org/standard/26522.html (last accessed 02-09-2022).
20. Washington State Department of Labor and Industries. Ergonomics. Olympia (WA): Washington State Department of Labor and Industries, 2000. WAC 296-62-051. Available at http://www.lni.wa.gov/Safety/Topics/Ergonomics/ServicesResources/Tools/default.asp. (last accessed 01-06-2022).
21. ISO 11226. ISO 11226:2000(en), Ergonomics - Evaluation of static working postures. 2000. Avaiable on line at: https://www.iso.org/standard/25573.html (last accessed 01-09-2022).
22. Waters TR, Putz-Anderson V, Garg A, Fine LJ. Revised NIOSH equation for the design and evaluation of manual lifting tasks. *Ergonomics*. 1993;36(7):749-776. Doi:10.1080/00140139308967940
23. Snook SH, Ciriello VM. The design of manual handling tasks: Revised tables of maximum acceptable weights and forces. *Ergonomics*. 1991;34(9):1197-1213. Doi:10.1080/00140139108964855
24. Apostoli P, Bazzini G, Sala E, Imbriani M. La versione italiana "OREGE" (Outil de Repérage et d'Evaluation des Gestes) dell'INRS (Institut national de recherche et de sécurité) per la valutazione dei disturbi muscolo-scheletrici dell'arto superiore [The Italian version of "OREGE" (Outil de Repérage et d'Evaluation des Gestes) of the INRS (Institut national de recherche et de sécurité) for the assessment of musculoskeletal disorders of the upper limb]. *G Ital Med Lav Ergon*. 2002;24(1):3-25.
25. Apostoli P, Sala E, Gullino A, Romano C. Analisi comparata dell'applicazione di quattro metodi per la valutazione del rischio biomeccanico per l'arto superiore [Comparative analysis of the use of 4 methods in the evaluation of the biomechanical risk to the upper limb]. *G Ital Med Lav Ergon*. 2004;26(3):223-241.
26. Cromie JE, Robertson VJ, Best MO. Work-related musculoskeletal disorders in physical therapists: prevalence, severity, risks, and responses. *Phys Ther*. 2000;80(4): 336-351. Doi:10.1093/ptj/80.4.336
27. Vieira ER, Schneider P, Guidera C, Gadotti IC, Brunt D. Work-related musculoskeletal disorders among physical therapists: A systematic review. *J Back Musculoskelet Rehabil*. 2016;29(3):417-428. Doi:10.3233/BMR-150649
28. Urwin M, Symmons D, Allison T, et al. Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation. *Ann Rheum Dis*. 1998;57(11):649-655. Doi:10.1136/ard.57.11.649
29. Ostör AJ, Richards CA, Prevost AT, Speed CA, Hazleman BL. Diagnosis and relation to general health of shoulder disorders presenting to primary care. Rheumatology. 2005;44:800-805. doi:10.1093/rheumatology/keh598
30. Brinkmann A, Fifelski C, Lau S, et al. Quantification of Lower Limb and Spine Muscle Activity in Manual Patient Handling - A Case Study. Stud Health Technol Inform. 2020;272:249-252. doi:10.3233/SHTI200541
31. Weber, B.; Douwes, M.; Forsman, M.; Könemann, R.; Heinrich, K.; Enquist, H.; Pinder, A.; Punakallio, A.; Uusitalo, A.; Ditchen, D.; et al. Assessing Arm Elevation at Work with Technical Systems; Partnership for European Research in Occupational Safety and Health: Sydney, NSW, Australia, 2018 DOI: 10.23775/20181201
32. Holder NL, Clark HA, DiBlasio JM, et al. Cause, prevalence, and response to occupational musculoskeletal injuries reported by physical therapists and physical therapist assistants. Phys Ther. 1999;79(7):642-652. doi:10.1093/ptj/79.7.642
33. Carta A, Parmigiani F, Parrinello G, Porru S. Fisioterapisti e disturbi muscoloscheletrici: analisi di una casistica [A survey on musculoskeletal disorders in physiotherapists]. G Ital Med Lav Ergon. 2007;29(3 Suppl):583-584.
34. Alrowayeh HN, Alshatti TA, Aljadi SH, Fares M, Alshamire MM, Alwazan SS. Prevalence, characteristics, and impacts of work-related musculoskeletal disorders: a survey among physical therapists in the State of Kuwait. BMC Musculoskelet Disord. 2010;11:116. Published 2010 Jun 11. doi:10.1186/1471-2474-11-116
35. Apostoli P, Cristaudo A, Violante FS: Linee guida per la Sorveglianza Sanitaria. SIML 2017; Nuova Editrice Berti, 2017.

Book review
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Nordberg G F, & Costa M. (Eds.). *Handbook on the toxicology of metals; volume I: general considerations* (5th ed.). Academic Press/Elsevier Amsterdam, Boston, 2022, pp. 796.
Nordberg G F, & Costa M. (Eds.). *Handbook on the toxicology of metals; volume II: specific metals* (5th ed.). Elsevier, London, 2022, pp. 1011.

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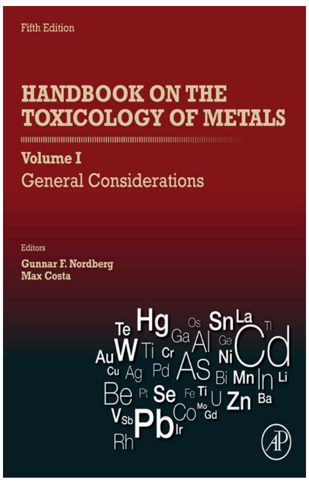

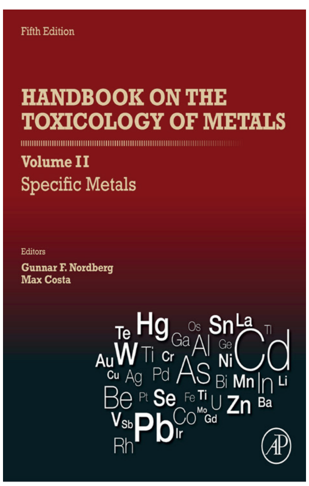

The *Handbook on the toxicology of metals*, now in its fifth edition, is a reference source of information for physicians, toxicologists, and engineers concerned with environmental and occupational health. Gunnar Nordberg, emeritus professor of Umeå University (Umeå, Sweden), has been among this book's editors since its first edition in 1979. Max Costa – Professor of the NYU School of Medicine (New York, USA) – is the co-editor of this new updated edition. As in previous editions, the *Handbook* is a comprehensive review of the effects on biological systems from metallic elements and their compounds, including the vast array of advancements made since the last edition. There are several new chapters, two on new metallic elements not covered by previous editions, and several chapters on general considerations. All chapters are updated, and the latest edition includes evidence of a newly recognized indium-related occupational disease and several new connections between metal exposures and illnesses. This up-to-date reference book provides easy access to basic toxicological concepts and critical aspects of metallic compounds' toxicology.

Handbook on the toxicology of metals, fifth edition, volume I: general considerations (30 chapters, 796 pp.) gives an overview and covers topics of general importance, including reviews of various health effects of trace metals, covering toxic effects in humans, along with discussions about the toxic impact of animals and biological systems in vitro when relevant. The book has been systematically updated with the latest advances in technology. As a multidisciplinary resource that integrates both human and environmental toxicology, the book is a comprehensive and valuable reference for toxicologists, physicians, pharmacologists, and environmental scientists in environmental, occupational, and public health.

Volume I comprises 30 chapters on general considerations such as the toxicity of metal nanoparticles, metals in food and metals, and air pollution (new chapter), as well as the toxicity of metals to various organ systems with new chapters on Respiratory effects and The Skin. It further includes considerations on the Ecotoxicology of Metals, describing sources, transport, and effects in the ecosystem. Other chapters in this volume focus on human health effects, both the beneficial effects of essential metals and the adverse effects of toxic metals in occupational and general environments. While the exposure has decreased for a few metals with recognized toxicity, for example, lead in the general environment, there is increased exposure to less studied metals. Considerable further increases in world production of several metals will occur in the next decades because of the demand by the transition to a fossil-free society required to halt climate change.

In recent times, increasing human exposures have occurred to metallic nanoparticles used for various purposes, including medical applications. Exposures also occur as chelates for MRI enhancement and releases from implanted medical devices, increasingly used for several medical purposes. Regardless of the source of human exposure, it is helpful to employ biological monitoring to get a quantitative estimate. Large programs are presently in place in some countries, monitoring large population groups' blood and urine concentrations of metals and other chemicals.

Handbook on the toxicology of metals, fifth edition, volume II: specific metals, (38 chapters, 1052 pp.) provides complete coverage of 38 individual metallic elements and their compounds. This volume emphasizes toxic effects in humans, along with discussions on the toxic effects of animals and biological systems in vitro when relevant.

Volume II reviews 38 specific metals and their compounds in separate chapters. Added new chapters are those on Osmium and Gadolinium, the latter metal involved in inducing the potentially life-threatening disease Nephrogenic Systemic Fibrosis when given to patients with impaired renal function as a chelate for enhancing Magnetic Resonance Imaging (MRI) procedures.

Clinically diagnosed occupational metal poisonings are rare in high-income countries. An exception is the recent recognition in the electronics industry in Japan and the USA of severe interstitial lung disease with alveolar proteinosis, sometimes leading to death, named Indium Lung Disease (ILD) or Indium lung, described in the chapter on Indium. Airborne, poorly soluble indium compounds such as indium tin oxide cause this disease. Chronic poisoning by mercury vapor with erethism, tremor, and other symptoms frequently occurs in artisanal small-scale gold mining in low – and lower-middle-income countries. According to estimates, under these circumstances, 1-2 million disease-adjusted life years (DALYs) are lost due to mercury poisoning, which also causes poisoning cases due to arsenic, lead, and cadmium.

In the general environment, widespread exposure to drinking water contaminated by inorganic arsenic occurs in several countries. Estimates for the situation in Bangladesh state thousands of deaths and more than a hundred thousand DALYs per year. From a worldwide perspective, estimates indicate one million illnesses, 56,000 deaths, and more than 9 million DALYs to be due to exposure to food-borne arsenic, methylmercury, lead, and cadmium.

These poisoning cases and other adverse health effects from too high exposures to toxic metals are in addition to global estimates of several hundred thousand deaths and millions of DALYs from zinc and iron deficiency. There is a need for intensified efforts in risk assessment and prevention, the subject of specific chapters in the *Handbook*.

All chapters have been written and peer-reviewed by experts – 116 contributors and 54 reviewers – which accounts for some inhomogeneity. The large number of collaborators involved as contributors and reviewers also testify to the efforts made to provide the best possible information quality in a field in continuous evolution, together with our ability to measure trace amounts of contaminants and the effects of their interactions with biological systems.

Antonio Mutti,
Editor in Chief

La Medicina del Lavoro

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Ricordo del Prof. Edoardo Gaffuri (1922-2022)

Lo scorso settembre, alla bella età di 100 anni, ci ha lasciato il Prof. Edoardo Gaffuri. Nato a Varese il 27 aprile 1922, si è laureato in Medicina all'Università di Padova nel 1947 per poi iniziare la sua carriera accademica e professionale come Assistente prima in Clinica Medica a Padova e, dal 1951 al 1956, a Torino sotto la direzione del Prof. Pio Bastai.

Ritornato a Padova come Assistente alla nuova Cattedra di Medicina del Lavoro, diretta dal Prof. Massimo Crepet, ha proseguito la sua carriera acquisendo la libera docenza in Medicina del Lavoro e in Semeiotica Medica. Nel 1971 gli è stato conferito l'insegnamento di Medicina del Lavoro presso la nuova sede universitaria di Verona, dove ha avviato e diretto l'Istituto di Medicina del Lavoro con la relativa Scuola di Specializzazione fino al pensionamento avvenuto nel 1995.

Il Prof. Edoardo Gaffuri è stato l'ultimo epigono dei padri fondatori della moderna Medicina del Lavoro italiana, catalizzatore lui stesso di una Scuola che negli anni Settanta e Ottanta del secolo scorso è stata un punto di riferimento nazionale di creatività e dinamismo, lasciando un segno profondo nello sviluppo della nostra disciplina.

Trasmetteva una elevata cultura umanistica e competenza medica, che traduceva in una rigorosa metodologia scientifica e comportamentale sia in campo clinico-diagnostico che nelle relazioni sociali.

Aveva una personalità complessa e un carattere a volte spigoloso, ma sempre orientato allo sviluppo della disciplina anche in modo pionieristico, a testimonianza della sua incessante attenzione all'evoluzione del mondo del lavoro nei suoi diversi aspetti sociali, politici, organizzativi e gestionali, con i quali la disciplina ha dovuto confrontarsi e riproporsi nella seconda metà del secolo scorso.

Lo ha fatto contribuendo in modo significativo alla trasformazione della Medicina del Lavoro da disciplina prevalentemente clinica, nel cui ambito si è distinto per importanti studi sulla fisiopatologia respiratoria e sulle broncopneumopatie croniche, a disciplina a orientamento preventivo, aprendo e garantendo lo sviluppo di innovative linee di ricerca in ambito igienistico-industriale, tossicologico e dei fattori di rischio psicosociali, sempre stimolando la curiosità scientifica e la rigorosa valutazione critica dei risultati ottenuti.

Lo ha fatto promuovendo la valenza e il ruolo sociale della nostra disciplina, valorizzando la partecipazione dei lavoratori e delle loro organizzazioni all'attività di tutela della salute nei luoghi di lavoro e riconoscendo anche il valore scientifico degli strumenti conoscitivi sui rischi lavoro correlati, da loro messi a punto.

Lo ha fatto garantendo la disseminazione accademica, istituzionale e divulgativa della Medicina del Lavoro e della Prevenzione in ambito regionale e nazionale, sia con il suo impegno diretto sia attraverso l'attività di molti suoi allievi che, dopo essersi formati nel suo Istituto e nella sua Scuola di specializzazione, sono stati chiamati a dirigere importanti Istituti, Centri e Servizi di Medicina del Lavoro in diverse regioni italiane.

Il Prof. Edoardo Gaffuri è stato un grande protagonista della Medicina del Lavoro italiana e la Società Scientifica di essa più rappresentativa non può che essergli riconoscente e inchinarsi alla sua memoria.

Pietro Apostoli
Giovanni Costa
Luigi Perbellini

La Medicina del Lavoro

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Leonardo Soleo (1948-2022)

L'improvvisa perdita del Prof. Leonardo Soleo ha colto di sorpresa e ha suscitato una grande tristezza in tutti coloro che lo hanno conosciuto come docente e come Collega impegnato nella promozione della nostra disciplina.

Il Prof. Soleo ha svolto l'intera carriera accademica, prima da studente e poi da ricercatore e docente, presso l'Università "Aldo Moro" di Bari, fino a diventare Professore ordinario di Medicina del Lavoro dal 2000 al 2018, anno del collocamento in quiescenza per raggiunti limiti d'età.

In questi ultimi vent'anni, il Prof. Soleo è stato uno dei protagonisti della nostra Società. Costante, rigoroso e appassionato è stato infatti il contributo alla nostra Società Scientifica sia in sede regionale che nazionale.

Il Prof. Soleo è stato Segretario nazionale della SIML durante tutti i mandati della Presidenza del Prof. Ambrosi nel primo decennio del 2000, in cui collaborò con un gruppo di colleghi alla promozione e alla redazione della prima serie di Linee Guida per l'aggiornamento e qualificazione dei medici del lavoro, in qualità di componente del comitato editoriale. Dell'attività in SIML durante il primo decennio di questo secolo si ricorda il suo impegno nel consolidamento della struttura societaria e la riunificazione in seno alla Società delle Associazioni settoriali che da essa si erano allontanate per assumere vita autonoma e indipendente nell'ultimo decennio del secolo scorso.

Prossimo alla conclusione della carriera accademica, ha organizzando l'81° Congresso Nazionale di Medicina del Lavoro (Bari, 26-28 settembre 2018).

Sotto il profilo scientifico, si è impegnato nella ricerca in Medicina del Lavoro con contributi in Tossicologia Industriale e Ambientale, con studi sull'esposizione e sugli effetti biologici di elementi metallici tossici nelle industrie siderurgica e aeronautica e nello studio delle relazioni tra inquinamento degli ambienti di lavoro e dell'ambiente generale di vita.

Sotto la direzione del Prof. Vito Foà, ha collaborato con la «La Medicina del Lavoro», poi divenuta rivista ufficiale della nostra Società, come membro del Consiglio di Redazione dal 2001 al 2015. Ha inoltre collaborato alla redazione di libri di testo e trattati di Medicina del Lavoro, contribuendo ai trattati coordinati da Duilio Casula (2003), Foà e Ambrosi (2003), al manuale di Medicina del Lavoro e Igiene Industriale di Lorenzo Alessio e Pietro Apostoli (2009) e al trattato coordinato da Lorenzo Alessio, Giuliano Franco e Francesco Tomei (2015).

Da chi ha avuto il privilegio di conoscerlo e lavorare con lui viene ricordato come figura generosa, sempre pronta e aperta alla collaborazione, convinta del ruolo e dell'importanza della Medicina del Lavoro. Colpiti e addolorati dalla sua prematura e improvvisa scomparsa, esprimiamo il nostro cordoglio alla famiglia e agli allievi della Scuola barese.

Giovanna Spatari, Presidente della Società Italiana di Medicina del Lavoro

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