RASSEGNE E ARTICOLI

Metabolic syndrome and risk of COVID-19-related hospitalization: a large, population-based cohort study carried out during the first European outbreak of SARS-CoV-2 infection in the Metropolitan area of Milan (Lombardy Region, Northern Italy)

Sindrome metabolica e rischio di ospedalizzazione: uno studio di coorte di popolazione effettuato nell'area metropolitana di Milano durante la prima ondata europea d'infezione da SARS-CoV-2

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WHAT IS ALREADY KNOWN

- **COVID-19 has a great variability of clinical presentations: it can run asymptomatic or have serious outcomes (hospitalization, death).**
- **Specific characteristics of the infected are associated with worse outcomes in case of COVID-19 infection.**
- **Age is the strongest predictor of hospitalization in case of COVID-19 infection.**

WHAT THIS STUDY ADDS

- **Subjects with one of the components of the metabolic syndrome (diabetes mellitus, dyslipidaemia, hypertension) are at greater risk of hospitalization in any ward when infected with SARS-CoV-2.**
- **The risk of hospitalization in any ward increases in an additive manner when more components are present in the same subject (up to 45% in the presence of all three components).**
- **Tra i soggetti già vaccinati con due dosi, il rischio di ricovero rimane più alto nella popolazione anziana e tra soggetti affetti da alcune patologie croniche specifiche.**
- **Subjects with uncomplicated diabetes mellitus have a risk increase of almost 40% of hospitalization in intensive care unit when infected with SARS-CoV-2.**

ABSTRACT

BACKGROUND: since the beginning of the COVID-19 pandemic, specific characteristics of the infected subjects appeared to be associated with a severe disease, leading to hospitalization or death.

OBJECTIVES: to evaluate the association between three components of the metabolic syndrome (diabetes mellitus, dyslipidaemia, and hypertension), alone and in combination, and risk of hospitalization in subjects with nasopharyngeal swab-confirmed COVID-19.

DESIGN: cohort study.

SETTING AND PARTICIPANTS: the study subjects were all COVID-19 cases diagnosed in the area of the Agency for Health Protection of the Metropolitan Area of Milan (Lombardy Region, Northern Italy) between 10.02.2020 and 25.04.2020, whose data were gathered with an ad hoc information system developed at the beginning of the pandemic.

MAIN OUTCOME MEASURES: the association between metabolic syndrome components (alone and in combination) and hospitalization (both in any ward and in intensive care unit) was measured by means of cause-specific Cox models with gender, age, and comorbidities as potential confounders.

RESULTS: the cohort included 15,162 subjects followed from diagnosis up to 20.07.2020. Adjusted hazard ratios (HRs) of hospitalization in any ward estimated by the Cox model were 1.26 for uncomplicated diabetes mellitus (95%CI 1.18-1.34); 1.21 for complicated diabetes mellitus (95%CI 1.05-1.39); 1.07 for dyslipidaemia (95%CI 1.00-1.14); and 1.11 for hypertension (95%CI 1.05-1.17). When all components coexisted in the same subject, the HR was 1.46 (95%CI 1.31-1.62). A significant increase in risk of hospitalization in intensive care unit was found for uncomplicated diabetes mellitus (HR 1.38; 95%CI 1.15-1.66).

CONCLUSIONS: this population-based study confirms that metabolic syndrome components increase the risk of hospitalization for COVID-19. The HR increases in an additive manner when the three components are simultaneously present.

Keywords: COVID-19, hospitalization (risk of), metabolic syndrome (as a risk factor)

RIASSUNTO

INTRODUZIONE: dall'inizio della pandemia di COVID-19, caratteristiche specifiche degli infetti sono parse associate con un decorso grave della malattia, implicante l'ospedalizzazione o la morte.

OBIETTIVI: valutare l'associazione fra tre componenti della sindrome metabolica (diabete mellito, dislipidemia e ipertensione arteriosa), prese singolarmente e in combinazione, e il rischio d'ospedalizzazione in soggetti con COVID-19 confermata mediante tampone rinofaringeo.

DISEGNO: studio di coorte.

SETTING E PARTECIPANTI: lo studio è stato condotto su tutti i casi di COVID-19 diagnosticati nell'area dell'Agenzia di tutela della salute di Milano fra il 10.02.2020 e il 25.04.2020. Le informazioni relative ai soggetti in studio sono state raccolte con un sistema informativo sviluppato ad hoc all'inizio della pandemia.

PRINCIPALI MISURE DI OUTCOME: l'associazione fra le componenti della sindrome metabolica (prese singolarmente e in combinazione) e l'ospedalizzione (sia in qualsiasi unità sia in unità di terapia intensiva) è stata stimata mediante

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modelli di Cox specifici per causa con genere, età e comorbidità come potenziali confondenti.
RISULTATI: la coorte includeva 15.162 soggetti seguiti dalla diagnosi fino al 20.07.2020. Il modello di Cox ha fornito le seguenti stime aggiustate degli hazard ratio (HR) di ospedalizzazione in qualsiasi reparto: 1,26 per il diabete mellito non complicato (IC95% 1,18-1,34); 1,21 per il diabete mellito complicato (IC95% 1,05-1,39); 1,07 per la dislipidemia (IC95% 1,00-1,14); e 1,11 per l'ipertensione arteriosa (IC95% 1,05-1,17). In presenza di tutte e tre le componenti della sindrome metabolica nello stesso soggetto, il modello ha stimato un HR aggiustato di 1,46 (IC95% 1,31-1,62). Un incremento significativo del rischio di ospedalizzazione in unità di terapia intensiva è stato riscontrato per il diabete mellito non complicato (HR 1,38; IC95% 1,15-1,66).
CONCLUSIONI: questo studio di popolazione conferma che la sindrome metabolica aumenta il rischio di ospedalizzazione nei soggetti affetti da COVID-19. L'incremento dell'HR è additivo in presenza di tutte e tre le componenti della sindrome nello stesso soggetto.

Parole chiave: COVID-19, ospedalizzazione (rischio di), sindrome metabolica (come fattore di rischio)

BACKGROUND

In late 2019, a cluster of viral pneumonia caused by a novel infectious agent, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in the Chinese city of Wuhan. The illness, named Coronavirus disease 2019 (COVID-19), rapidly spread to the whole of China and, within a few months, to Europe and the US, causing a health emergency with a global impact on society and economy. COVID-19 mortality risk estimates vary between 2.3 and 3.0%,[1,2] but the infectiousness is high, with a basic reproduction number (R_0) greater than those of SARS and MERS. First R_0 estimates ranged from 2.2 to 2.7,[3] compared to R_0 between 1.7 and 1.9 for SARS and < 1 for MERS.[1] However, later estimates that included the role of so-called 'super-spreaders' ranged from 4.7 to 11.4,[4] leading to a serial interval estimate of 5.2 days.[5]
The first autochthonous case in Italy was diagnosed on 20.02.2020 in Codogno, a municipality close to the metropolitan area of Milan. The spread was rapid and uncontrolled, and on the 9th of March a nationwide lockdown was imposed. The R_t dropped below one in the metropolitan area of Milan on the 23rd of March,[6] but it took nearly two months for the hospitals, overwhelmed by hospitalized moderate and severe cases, to return to normal operation.
Since the very beginning of the epidemic, specific individual characteristics of the infected subjects, such as old age and comorbidities, appeared to be associated with a more severe disease.[7] The metabolic syndrome or its components were associated with a higher risk of hospitalization or death in several studies.[8-13] Although different definitions of metabolic syndrome do exist, the definition of the International Diabetes Federation[14] includes central obesity and two or more of the following: • raised triglycerides; • reduced HDL-cholesterol; • raised blood pressure; • raised fasting plasma glucose or • previously diagnosed type 2 diabetes. It has been hypothesized that the low-grade chronic systemic inflammation with elevated interleukin 6, which is typical of metabolic syndrome, provides a favourable ambiance for the development of the so-called 'cytokine storm' in case of infection. Moreover, the greater expression of the angiotensin-converting enzyme 2 in obese people might facilitate the infection and also induce severe COVID-19 by promoting the diffusion of SARS-CoV-2 in the body.[15,16]
The purpose of this study is to estimate the impact of three components of the metabolic syndrome (i.e., diabetes mellitus, dyslipidaemia, and hypertension), individually and in combination, on the risk of hospitalization in subjects with nasopharyngeal swab-confirmed COVID-19. These components have been chosen as they can be reliably derived with the algorithms of the Lombardy region (Northern Italy)[17] from current health databases. A retrospective population-based cohort study was performed in the territory of the Metropolitan area of Milan.

METHODS

A population-based cohort design was adopted in which subjects were followed from the diagnosis of COVID-19 up to 20.07.2020. The cohort includes all COVID-19 cases diagnosed in the area of the Agency for Health Protection of the Metropolitan area of Milan (ATS). This corresponds to 193 municipalities in the Northern Italian region of Lombardy, with a total population of 3.5 million inhabitants.[18] It includes the city of Milan, which is the second-largest city in Italy, and the municipality of Codogno, where the Italian outbreak of COVID-19 started.
Confirmed cases of COVID-19 and their contacts were traced by the ATS from the beginning of the epidemic, and all tracing-related information were entered in a web-based platform called *Milano COV*. A confirmed case was defined as a person with a nasopharyngeal swab-confirmed SARS-CoV-2 infection, irrespective of clinical signs and symptoms.
For analysis purposes, *Milano COV* data were verified, comparing them with demographic information contained in the Regional Health Database of Lombardy (age, gender, and place of residence of subjects); then anonymized, assigning a random unique id to each subject; and finally assembled in an integrated data warehouse for COVID-19 analyses.
For the purposes of this study, all subjects who were diagnosed with SARS-CoV-2 infection between 10.02.2020

and 25.04.2020 were extracted from the data warehouse for COVID-19 analyses, with the relative information about gender and age. Data on hospitalization were acquired as follows. Lombardy Region sends daily to its constituents ATSs the list of hospitalized COVID-19 cases: it contains the date of entry and the name of the hospital where the patient was admitted, and variations (transfer, home discharge, death) are communicated in the following day dataflow. Additional information relating to hospitalizations of patients with COVID-19 were derived from the regular administrative dataflow of discharges. A detailed description of the whole outbreak reporting system and its aims have already been published.[6,17,19] Information about metabolic syndrome components and other chronic conditions were derived from the database of chronic diseases of the ATS, according to the algorithms specified in the deliberations of Lombardy Region X/6164[20] and X/7655[21] of 2017. These algorithms, based on hospital discharge records, outpatient visits, drug prescriptions, and copayment exemptions databases can be found in full in Murtas et al.[17] and are summarized, limited to the conditions which have been considered in this study, in Table S1.

Residents in nursing home at the time of diagnosis were excluded from the analyses. The ATS does not acquire health status information from facilities dedicated to long-term care comparable to those of the health databases that are used to identify comorbidities. Consequently, presence of chronic conditions is underestimated in this population. Moreover, hospitalization kinetics of patients of facilities dedicated to terminal cares are very different from those of the general population. As a rule, hospitalization is not carried out due to terminality and regardless of other individual characteristics.

The relationship between the metabolic syndrome components and risk of hospitalization in any acute ward was analysed accounting for the competitive risk of death, first considering the presence of each component and then the number of components (0-3) afflicting each subject. Demographic and health status potential confounders were accounted for. With the same approach, the relationship between subjects' characteristics and hospitalization in intensive care unit (ICU) was then explored. In this case, the event of interest was defined as the hospitalization in ICU (direct or following hospitalization in non-ICU), while competing events were hospitalization in non-ICU (never followed by hospitalization in ICU) and death. Only COVID-19-related hospitalizations were considered and, if one or more of them were recorded for a subject, the date of admission of the first one was set as the event date.

STATISTICAL METHODS

Median follow-up time was calculated using the reverse Kaplan-Meier estimator. The characteristics of the cohort were described by means of frequencies and proportions. To analyse the risk of hospitalization, the cumulative incidence functions (CIFs) for hospitalization in any ward, hospitalization in non-ICU, and hospitalization in ICU were first estimated. Multicollinearity between comorbidities was then excluded by calculating the generalized variance inflation factors, all of which resulted <2. The association between metabolic syndrome components and hospitalization in any ward was evaluated by means of univariate and multivariable cause-specific Cox models, after graphical evaluation of the following function

$$\log \{-\log [S(t)]\}$$

and testing for the proportional hazards assumption.[22] No relevant violations of the assumption were found for the components of the metabolic syndrome and for the other chronic conditions. The assumption did not hold for gender and age group, consequently all multivariable Cox models were stratified for these variables. The investigated components of the metabolic syndrome were diabetes mellitus (DM), dyslipidaemia, and hypertension. Uncomplicated and complicated DM were considered as two distinct independent variables when taking into account the components of the metabolic syndrome as separate variables, while DM was considered as a single disease when taking into account the number of components afflicting each subject. The other 6 individual characteristics included in the multivariable models were comorbidities which, based on literature,[23-26] have a recognized association with severe COVID-19 and possibly with metabolic syndrome: • cardiovascular diseases; • chronic obstructive pulmonary disease; • respiratory failure; • asthma; • chronic kidney disease; • dialysis. By means of the described regression models, the hazard ratios (HRs) of hospitalization for the metabolic syndrome components alone and in combinations, with their 95% confidence intervals (95%CIs), were estimated. The association between individual metabolic syndrome components and hospitalizations in ICU was measured with the same methodology and considering the same confounding factors.

Data management was carried out in SAS 9.4 (SAS Institute, Cary, North Carolina, USA), while analyses were performed in R 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria), respectively.

RESULTS

The cohort included 15,162 subjects with nasopharyngeal swab-confirmed COVID-19 who were followed for 836,816 person-days when considering hospitalization in any ward as the event of interest, and 837,338 person-days considering hospitalization in non-ICU and hospitalization in ICU as distinct events. Median follow-up time was

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CHARACTERISTCS	CATEGORIES	SUBJECTS	
		n.	%
Gender	Females	7,159	47.22
	Males	8,003	52.78
Age group (years)	0-19	187	1.23
	20-39	1,788	11.79
	40-44	934	6.16
	45-49	1,376	9.08
	50-54	1,599	10.55
	55-59	1,640	10.82
	60-64	1,314	8.67
	65-69	1,048	6.91
	70-74	1,203	7.93
	75-79	1,301	8.58
	80-84	1,298	8.56
	≥85	1,474	9.72
Metabolic syndrome components			
Uncomplicated diabetes mellitus	Yes	1,698	11.20
Complicated diabetes mellitus	Yes	287	1.89
Dyslipidaemia	Yes	1,773	11.69
Hypertension	Yes	5,696	37.57
Number of metabolic syndrome components (afflicting the same subject)	0	8,706	57.42
	1	4,060	26.78
	2	1,803	11.89
	3	593	3.91
Comorbidities			
Cardiovascular diseases	Yes	3,062	20.20
Chronic obstructive pulmonary disease	Yes	606	4.00
Respiratory failure	Yes	40	0.26
Asthma	Yes	398	2.62
Chronic kidney disease	Yes	354	2.33
Dialysis	Yes	131	0.86
Total		15,162	100

Table 1. Distribution of nasopharyngeal swab-confirmed cases of COVID-19 diagnosed between 10.02.2020 and 25.04.2020 in the provinces of Milan and Lodi (Northern Italy), by gender, age group, and chronic conditions.
Tabella 1. Distribuzione dei casi di COVID-19 diagnosticati mediante tampone rinofaringeo fra il 10.02.2020 e il 25.04.2020 nelle province di Milano e Lodi (Lombardia), per genere, fascia di età e cronicità.

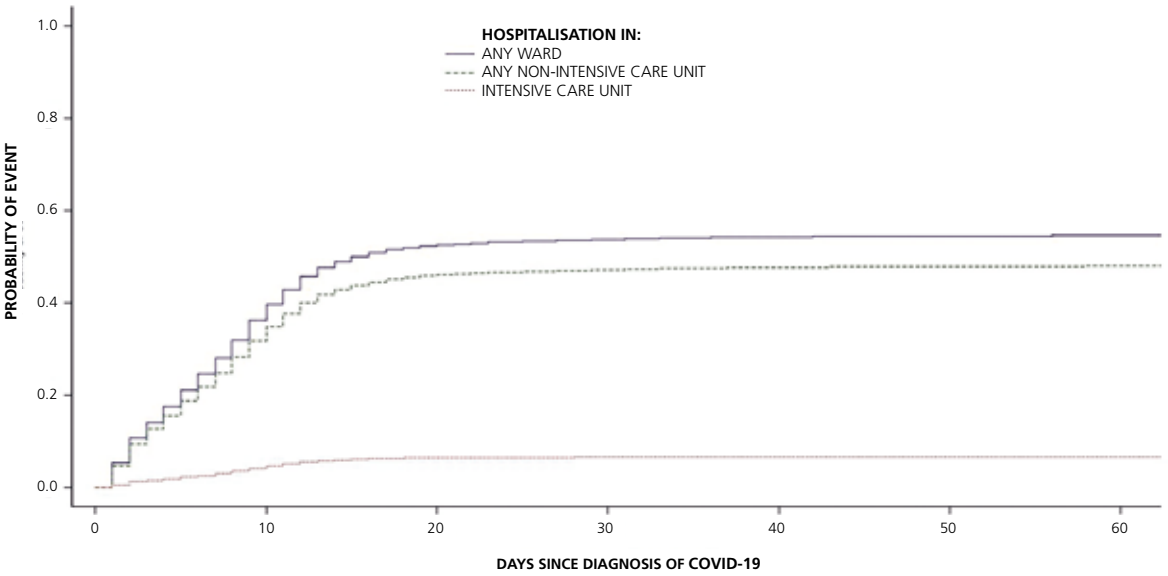
NOTE: Subjects who were residing in nursing home at diagnosis have been excluded.
NOTA: *I soggetti residenti in RSA alla diagnosi sono stati esclusi.*

123 days (95%CI 122-123 days). The maximum observation time from diagnosis to event was 162 days for any observation, 141 days for death, 100 days for hospitalization in non-ICU, and 74 days for hospitalization in ICU. Males were the slight majority (52.8%) (Table 1). About 40% of subjects were 65 years or older (compared to less than 25% in the general population of the ATS);[18] almost 20% were 80 years or older (about 7% in the general population);[18] and only 1.2% were 19 or younger (almost 18% in the general population).[18] 42.6% of subjects had at least one metabolic syndrome component, 15.8% at least two, and 3.9% all three components. DM (uncomplicated or complicated) was present in 13.1% of subjects, dyslipidaemia in 11.7%, and hypertension in 37.6%. Among comorbidities, the most prevalent were overt cardiovascular diseases (20.2%). Characteristics of subjects with and without each metabolic syndrome component are detailed in Tables S2-S5.

Overall, 6,858 subjects (45.2%) were never hospitalized, while 8,304 (54.8%) were hospitalized at least once; 7,298 subjects (87.9% out of 8,304 hospitalized) were hospitalized in non-ICU and 1,006 (12.1%) were hospitalized in ICU (directly or after hospitalization in non-ICU). Of all subjects, 585 (3.9%) died during the observation time.

The crude CIFs of hospitalization in any ward, in non-ICU, and in ICU at 21 days were 52.7% (95%CI 51.9-53.5%), 46.2% (95%CI 45.4-47.0%), and 6.4% (95%CI 6.1-6.8%), respectively. For each of these events, the probability that it occurred at a certain time increases remarkably in the first two weeks since diagnosis and reaches a plateau by the end of the third week (Figure 1).

Results from the univariate and multivariable analyses of association between metabolic syndrome components (separately and as a single variable counting the number of components) and COVID-19-related hospitalization in any ward estimated by the Cox models are reported in



NOTE: Subjects who were residing in nursing home at diagnosis have been excluded. / ***NOTA:*** *I soggetti residenti in RSA alla diagnosi sono stati esclusi.*

Figure 1. Graphical depiction of cumulative incidence functions for COVID-19-related hospitalization in subjects with nasopharyngeal swab-confirmed SARS-CoV-2 infection diagnosed between 10.02.2020 and 25.04.2020 in the provinces of Milan and Lodi (Northern Italy).
Figura 1. Rappresentazione grafica delle incidenze crude cumulative di ospedalizzazione per COVID-19 nei soggetti con infezione da SARS-CoV-2 diagnosticata mediante tampone rinofaringeo fra il 10.02.2020 e il 25.04.2020 nelle province di Milano e Lodi (Lombardia).

Table 2. According to the multivariable Cox model, significant increases in risk were found for subjects with the following metabolic syndrome components: uncomplicated DM, having an increase in risk of about 25% (HR 1.26; 95%CI 1.18-1.34); complicated DM, having an increase in risk of about 20% (HR 1.21; 95%CI 1.05-1.39); dyslipidaemia, having a 7% increased risk (HR 1.07; 95%CI 1.00-1.14); and hypertension, having an increase in risk of about 10% (HR 1.11; 95%CI 1.05-1.17). In the model including metabolic syndrome as a single variable, the HRs, compared to the absence of all components, were 1.17 (95%CI 1.11-1.24) for the presence of a single component; 1.31 (95%CI 1.22-1.41) for two components; and 1.46 (95%CI 1.31-1.62) for the presence of the syndrome, i.e., all three components. Among potential confounders, risk increases were found in those with obstructive lung diseases, with increases in risk of 13% for COPD (HR 1.13; 95%CI 1.02-1.24) and of 16% for asthma (HR 1.16, 95%CI 1.02-1.32). Results from separate models for female and male (Table S6 and Table S7) showed similar increases in risk of hospitalization for uncomplicated DM (HR 1.23; 95%CI 1.09-1.37 in females and HR 1.26; 95%CI 1.17-1.36 in males); risk increases for complicated DM higher in males (HR 1.24; 95%CI 1.05-1.47 vs HR 1.14; 95%CI 0.89-1.46 in females); and risk increases somewhat higher in females for both dyslipidaemia (HR 1.10; 95%CI 0.98-1.23 vs HR 1.06; 95%CI 0.98-1.15 in males) and hypertension (HR 1.17; 95%CI 1.07-1.28 vs HR 1.07; 95%CI 1.00-1.15 in males).

The HRs of COVID-19-related hospitalization in ICU are shown in Table 3. The only metabolic syndrome component with a significantly increased risk was, according to the multivariable Cox model, uncomplicated DM, having an increase in risk of almost 40% (HR 1.38; 95%CI 1.15-1.66). In the Cox model including metabolic syndrome as a single variable counting the number of components, significant increases in risk of about 30% and 55% were found when one or two components were present in the same subject compared to no components (HR 1.29; 95%CI 1.11-1.50 for one component and HR 1.57; 95%CI 1.28-1.94 for two). Only 32 subjects with the complete syndrome were hospitalized in ICU. Results from separate models for female and male (Table S8 and Table S9) showed significant risk increases for uncomplicated DM in both females (HR 1.65; 95%CI 1.09-2.47) and males (HR 1.33; 95%CI 1.08-1.64) and hypertension in females (HR: 1.47; 95%CI 1.08-2.01 vs HR 1.06; 95%CI 0.90-1.26 in males).

DISCUSSION

The results of this study, obtained on a large population of infected subjects, confirm the role of the individual components of metabolic syndrome and of their combination as main risk factors for COVID-19-related hospitalization. DM, dyslipidaemia, and hypertension have been already recognised as risk factors both as individual comorbidities[10,12,27,28] and in the more general context of the metabolic syndrome.[8,29,30] Recent meta-ana-

CHARACTERISTICS	CATEGORIES	INCIDENT CASES OF HOSPITALIZATION IN ANY UNIT (TOTAL SUBJECTS)[a]		HR	(95%CI)	HR	(95%CI)
Metabolic syndrome components							
Uncomplicated diabetes mellitus	No	7,049	(13,473)	Reference		Reference	
	Yes	1,255	(1,698)	1.93[b]	(1.82-2.05)[b]	1.26[c]	(1.18-1.34)[c]
Complicated diabetes mellitus	No	8,085	(14,875)	Reference		Reference	
	Yes	219	(287)	2.09[b]	(1.83-2.39)[b]	1.21[c]	(1.05-1.39)[c]
Dyslipidaemia	No	6,979	(13,389)	Reference		Reference	
	Yes	1,325	(1,773)	1.97[b]	(1.86-2.09)[b]	1.07[c]	(1.00-1.14)[c]
Hypertension	No	4,278	(9,466)	Reference		Reference	
	Yes	4,026	(5,696)	2.12[b]	(2.03-2.22)[b]	1.11[c]	(1.05-1.17)[c]
Number of metabolic syndrome components (afflicting the same subject)	0	3,773	(8,706)	Reference		Reference	
	1	2,704	(4,060)	1.96[b]	(1.87-2.06)[b]	1.17[d]	(1.11-1.24)[d]
	2	1,360	(1,803)	2.66[b]	(2.50-2.83)[b]	1.31[d]	(1.22-1.41)[d]
	3	467	(593)	3.12[b]	(2.84-3.44)[b]	1.46[d]	(1.31-1.62)[d]
Comorbidities							
Cardiovascular diseases	No	6,093	(12,100)			Reference	
	Yes	2,211	(3,062)			1.01[c]	(0.95-1.07)[c]
Chronic obstructive pulmonary disease	No	7,837	(14,556)			Reference	
	Yes	467	(606)			1.13[c]	(1.02-1.24)[c]
Respiratory failure	No	8274	(15,122)			Reference	
	Yes	30	(40)			0.95[c]	(0.66-1.36)[c]
Asthma	No	8,074	(14,764)			Reference	
	Yes	230	(398)			1.16[c]	(1.01-1.32)[c]
Chronic kidney disease	No	8,038	(14,808)			Reference	
	Yes	266	(354)			1.02[c]	(0.90-1.16)[c]
Dialysis	No	8,212	(15,031)			Reference	
	Yes	92	(131)			1.05[c]	(0.85-1.29)[c]
Total		8,304	(15,162)				

HR: hazard ratio / *hazard ratio*

NOTE: Subjects who were residing in nursing home at diagnosis have been excluded. / ***NOTA:*** *I soggetti residenti in RSA alla diagnosi sono stati esclusi.*

[a] Incident cases of hospitalization in any unit for COVID-19 from 10.02.2020 to 20.07.2020. / *Casi incidenti d'ospedalizzazione per COVID-19 in qualsiasi unità dal 10.02.2020 al 20.07.2020.*

[b] Hazard ratios and the corresponding 95% confidence intervals were calculated using univariate Cox models, each including as sole independent variable a single component of the metabolic syndrome or a variable whose modalities corresponded to the number of components. / *Gli hazard ratio e i corrispondenti intervalli di confidenza al 95% sono stati calcolati attraverso modelli di Cox univariati, ognuno dei quali comprendente come unica variabile indipendente una singola componente della sindrome metabolica oppure una variabile le cui modalità corrispondevano al numero di componenti.*

[c] Hazard ratios and corresponding 95% confidence intervals were calculated from multivariable Cox models stratified for gender and age groups and including each component of the metabolic syndrome as a separate variable and the chronic conditions as independent variables. / *Gli hazard ratio e i corrispondenti intervalli di confidenza al 95% sono stati calcolati attraverso un modello di Cox multivariabile stratificato per fasce di età includendo separatamente le componenti della sindrome metabolica oltre alle comorbidità come variabili indipendenti.*

[d] Hazard ratios and corresponding 95% confidence intervals were calculated from multivariable Cox models stratified for gender and age groups and including the metabolic syndrome as a numeric variable counting the present components for each subject and the chronic conditions as independent variables. HRs of chronic conditions from this second model are not presented. / *Gli hazard ratio e i corrispondenti intervalli di confidenza al 95% sono stati calcolati attraverso un modello di Cox multivariabile stratificato per fasce di età includendo la sindrome metabolica come numero di componenti per soggetto oltre alle comorbidità come variabili indipendenti. Gli HR delle comorbidità di questo modello non sono riportati in tabella.*

Table 2. Analysis of the association between metabolic syndrome component and hospitalization in any unit in the cohort with nasopharyngeal swab-confirmed SARS-CoV-2 infection diagnosed between 10.02.2020 and 25.04.2020 in the provinces of Milan and Lodi (Northern Italy).
Tabella 2. Analisi dell'associazione tra le componenti della sindrome metabolica e ospedalizzazione in qualunque reparto nella coorte con infezione da SARS-CoV-2 diagnosticata mediante tampone rinofaringeo fra il 10.02.2020 e il 25.04.2020 nelle province di Milano e Lodi (Lombardia).

CHARACTERISTICS	CATEGORIES	INCIDENT CASES OF HOSPITALIZATION IN INTENSIVE CARE UNIT (TOTAL SUBJECTS)[a]		HR	(95%CI)	HR	(95%CI)
Metabolic syndrome components							
Uncomplicated diabetes mellitus	No	856	(13,473)	Reference		Reference	
	Yes	150	(1,698)	1.89[b]	(1.59-2.25)[b]	1.38[c]	(1.15-1.66)[c]
Complicated diabetes mellitus	No	990	(14,875)	Reference		Reference	
	Yes	16	(287)	1.24[b]	(0.76-2.04)[b]	0.98[c]	(0.59-1.64)[c]
Dyslipidaemia	No	880	(13,389)	Reference		Reference	
	Yes	126	(1,773)	1.48[b]	(1.22-1.78)[b]	1.03[c]	(0.84-1.27)[c]
Hypertension	No	586	(9,466)	Reference		Reference	
	Yes	420	(5,696)	1.60[b]	(1.41-1.82)[b]	1.14[c]	(0.98-1.32)[c]
Number of metabolic syndrome components (afflicting the same subject)	0	506	(8,706)	Reference		Reference	
	1	320	(4,060)	1.28[b]	(1.10-1.49)[b]	1.29[d]	(1.11-1.50)[d]
	2	148	(1,803)	1.58[b]	(1.28-1.94)[b]	1.57[d]	(1.28-1.94)[d]
	3	32	(593)	1.12[b]	(0.76-1.64)[b]	1.11[d]	(0.76-1.62)[d]
Comorbidities							
Cardiovascular diseases	No	830	(12,100)			Reference	
	Yes	176	(3,062)			0.83[c]	(0.69-1.01)[c]
Chronic obstructive pulmonary disease	No	977	(14,556)			Reference	
	Yes	29	(606)			0.89[c]	(0.61-1.30)[c]
Respiratory failure	No	1,003	(15,122)			Reference	
	Yes	3	(40)			0.99[c]	(0.32-3.09)[c]
Asthma	No	982	(14,764)			Reference	
	Yes	24	(398)			0.93[c]	(0.62-1.40)[c]
Chronic kidney disease	No	986	(14,808)			Reference	
	Yes	20	(354)			0.89[c]	(0.57-1.40)[c]
Dialysis	No	1,003	(15,031)			Reference	
	Yes	3	(131)			0.30[c]	(0.10-0.94)[c]
Total		1,006	(15,162)				

HR: hazard ratio / *hazard ratio*

NOTE: Subjects who were residing in nursing home at diagnosis have been excluded. / ***NOTA:*** *I soggetti residenti in RSA alla diagnosi sono stati esclusi.*

[a] Incident cases of hospitalization in intesive care unit for COVID-19 from 10.02.2020 to 20.07.2020. / *Casi incidenti d'ospedalizzazione per COVID-19 in unità di terapia intensiva dal 10.02.2020 al 20.07.2020.*

[b] Hazard ratios and the corresponding 95% confidence intervals were calculated using univariate Cox models, each including as sole independent variable a single component of the metabolic syndrome or a variable whose modalities corresponded to the number of components. / *Gli hazard ratio e i corrispondenti intervalli di confidenza al 95% sono stati calcolati attraverso modelli di Cox univariati, ognuno dei quali comprendente come unica variabile indipendente una singola componente della sindrome metabolica oppure una variabile le cui modalità corrispondevano al numero di componenti.*

[c] Hazard ratios and corresponding 95% confidence intervals were calculated from multivariable Cox models stratified for gender and age groups and including each component of the metabolic syndrome as a separate variable and the chronic conditions as independent variables. / *Gli hazard ratio e i corrispondenti intervalli di confidenza al 95% sono stati calcolati attraverso un modello di Cox multivariabile stratificato per fasce di età includendo separatamente le componenti della sindrome metabolica oltre alle comorbidità come variabili indipendenti.*

[d] Hazard ratios and corresponding 95% confidence intervals were calculated from multivariable Cox models stratified for gender and age groups and including the metabolic syndrome as a numeric variable counting the present components for each subject and the chronic conditions as independent variables. HRs of chronic conditions from this second model are not presented. / *Gli hazard ratio e i corrispondenti intervalli di confidenza al 95% sono stati calcolati attraverso un modello di Cox multivariabile stratificato per fasce di età includendo la sindrome metabolica come numero di componenti per soggetto oltre alle comorbidità come variabili indipendenti. Gli HR delle comorbidità di questo modello non sono riportati in tabella.*

Table 3. Analysis of the association between metabolic syndrome component and hospitalization in intensive care unit in the cohort with nasopharyngeal swab-confirmed SARS-CoV-2 infection diagnosed between 10.02.2020 and 25.04.2020 in the provinces of Milan and Lodi (Northern Italy).
Tabella 3. Analisi dell'associazione tra le componenti della sindrome metabolica e ospedalizzazione in terapia intensiva nella coorte con infezione da SARS-CoV-2 diagnosticata mediante tampone rinofaringeo fra il 10.02.2020 e il 25.04.2020 nelle province di Milano e Lodi (Lombardia).

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lyses estimated a severe COVID-19 odds ratio of 2.5-2.8 for diabetic versus non-diabetic subjects,[10,31] while a 20%-25% hazard increase was found for the diabetics with and without complications. For dyslipidaemia, a 7% increase in risk of hospitalization was found, while a recent meta-analysis[12] estimated a 40% risk increase of severe COVID-19. Concerning hypertension, a HR of hospitalization of 1.11 was found, while a meta-analysis estimated an odds ratio of 2.5 of severe COVID-19.[32] However, it should be noted that the present study did correct for more possible confounders than most of the meta-analysed studies regarding the three metabolic syndrome components. It is also possible that the use of administrative databases to identify the components of the metabolic syndrome slightly underestimates their prevalence. The estimated concordance between the prevalence of metabolic syndrome components derived from the administrative databases and the validation from general practitioners of the ATS is between 90% (dyslipidaemia) and 98% (hypertension, unpublished data).

Several possible pathogenic mechanisms related to metabolic conditions have been proposed to explain the association between them and severe COVID-19, among which the most accredited are dysregulation of angiotensin-converting enzyme 2 (that is the receptor acting as entry point for SARS-CoV-2 in human cells), dysfunctions of liver and endothelium, and a chronic proinflammatory and procoagulant state.[11,16,29]

The association between metabolic syndrome and COVID-19 severity poses an important public health problem. The prevalence of the metabolic syndrome components in 2020 in the adult population of the ATS, estimated from administrative databases, is 7.2% for DM (N. 212,192), 7.1% for dyslipidaemia (N. 209,243), and 23.8% for hypertension (N. 686,671), summing to 805,623 individuals. The subjects with all three components are 1.7% of the adult population of the ATS (N. 48,258 subjects) according to data from administrative databases, but this approach clearly underestimates the expected prevalence (which is around 20%),[33] because only the most serious cases can be detected with it (i.e., glucose intolerance is missed and the additional criterion of waist circumference cannot be assessed). According to data from administrative databases, in the ATS the number of adult subjects with at least two components is 203,006. In the studied cohort, including all subjects with a confirmed diagnosis of COVID-19 in the ATS during the first epidemic wave, the percentages of subjects with the same diagnoses were consistently higher, even if people under the age of 18 were not excluded (3.9% metabolic syndrome, 37.6% hypertension, 13.1% diabetes and 11.7% dyslipidaemia). Hypertension alone increases the risk of hospitalization by 10%, but this applies to about 700,000 people, having two components increases the risk by 30% applying to about 200,000 peoples, and the whole syndrome as defined from administrative databases increases the risk by 46% applying to about 50,000 peoples. Consequently, to avoid overwhelming of the hospital system, targeted preventive campaigns, both at population and at primary care levels, should be implemented in the short run to increase risk awareness, adherence to ongoing treatment, and acceptance of vaccination not only in subjects with metabolic syndrome (who, though relatively small in number, are at high risk), but also in all subjects with DM, dyslipidaemia, and hypertension alone, which carry a lower risk of hospitalization, but whose prevalence is higher in the population.[34] This also applies to younger people, which may not feel to be at risk for a severe form of COVID-19 and for being hospitalized.[35]

A major strength of this study is the involvement of a very large number of subjects, which was made possible by the use of public health service databases and ad hoc efficient information systems set up during the emergency. A limitation of this study is the lack of anthropometric measures, such as waist circumference and BMI, which would have allowed to include in the models a canonically-defined metabolic syndrome[36] instead of its components. Evidence exists, indeed, that the metabolic syndrome is a better predictor of risk than its separate components,[13] even if in the present study the effect of the presence of the three components was additive on the HR scale. Another limitation is the lack of results of diagnostic tests (such as the actual values of blood lipids concentration or of arterial pressure), which would have made it possible to estimate increases in risk for meaningful units of increase (e.g., for mmHg of arterial blood pressure) instead of 'high' versus 'normal' using a single cut-off.

CONCLUSIONS

This study corroborates, in a large cohort of confirmed cases, the role of the components of the metabolic syndrome (and especially of the combination of them) in increasing the risk of COVID-19-related hospitalization, accounting for a number of potential confounders. This finding should be considered when planning public health measures. Being already known the increases in risk of developing overt cardiovascular diseases and malignant tumours of subjects with metabolic syndrome, it especially renews the calls for interventions aimed at adequately informing these individuals of their augmented risks and at modifying the behaviours at the base of the syndrome even in young adults.

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