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Diabetes is most important cause for mortality in COVID-19 hospitalized patients: Systematic review and meta-analysis

Giovanni Corona[1] · Alessandro Pizzocaro[2] · Walter Vena[2] · Giulia Rastrelli[3] · Federico Semeraro[4] · Andrea M Isidori[5] · Rosario Pivonello[6,7] · Andrea Salonia[8,9] · Alessandra Sforza[1] · Mario Maggi[10]

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Abstract

The presence of SARS-CoV-2 was officially documented in Europe at the end of February 2020. Despite many observations, the real impact of COVID-19 in the European Union (EU), its underlying factors and their contribution to mortality and morbidity outcomes were never systematically investigated. The aim of the present work is to provide an overview and a meta-analysis of main predictors and of country differences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection-associated mortality rate (MR) in hospitalized patients. Out of 3714 retrieved articles, 87 studies were considered, including 35,486 patients (mean age 60.9 ± 8.2 years) and 5867 deaths. After adjustment for confounders, diabetes mellitus was the best predictors of MR in an age- and sex-dependent manner, followed by chronic pulmonary obstructive diseases and malignancies. In both the US and Europe, MR was higher than that reported in Asia (25[20;29] % and 20[17;23] % vs. 13[10;17]%; both $p < 0.02$). Among clinical parameters, dyspnea, fatigue and myalgia, along with respiratory rate, emerged as the best predictors of MR. Finally, reduced lymphocyte and platelet count, along with increased D-dimer levels, all significantly contributed to increased mortality. The optimization of glucose profile along with an adequate thrombotic complications preventive strategy must become routine practice in diseased SARS-CoV-2 infected patients.

Keywords Diabetes mellitus · SARS-CoV-2 · COVID-19 · male · testosterone · mortality · hospitalization

1 Introduction

Between late 2019 and early 2020 a novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was isolated in the city of Wuhan in China [1–4]. Thereafter, the virus has rapidly spread around the world causing a novel type of disease named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) in February 2020 [4]. The clinical manifestations of COVID-19 are quite variable ranging from an asymptomatic condition to life-threatening SARS and death [1–4]. From its first description and isolation, the SARS-CoV-2 infection rapidly spread worldwide,

✉ Giovanni Corona
jocorona@libero.it

1 Endocrinology Unit, Medical Department, Azienda Usl Bologna Maggiore-Bellaria Hospital, Largo Nigrisoli, 2 - 40133 Bologna, Italy

2 Unit of Endocrinology, Diabetology and Medical Andrology, IRCSS, Humanitas Research Hospital, Rozzano, Milan, Italy

3 Female Endocrinology and Gender Incongruence Unit, Department of Experimental, Clinical and Biomedical Sciences, University of Florence, Florence, Italy

4 Department of Anaesthesia, Intensive Care and EMS, Maggiore Hospital Bologna, Bologna, Italy

5 Department of Experimental Medicine, Sapienza University of Rome - Policlinico Umberto I Hospital, Rome, Italy

6 Dipartimento Di Medicina Clinica E Chirurgia, Sezione Di Endocrinologia, Unità Di Andrologia E Medicina Della Riproduzione E Della SessualitàMaschile E Femminile, Università Federico II Di Napoli, Naples, Italy

7 Staff of UNESCO, Chair for Health Education and Sustainable Development, Federico II University, Naples, Italy

8 Division of Experimental Oncology/Unit of Urology, URI, IRCCS Ospedale San Raffaele, Milan, Italy

9 University Vita-Salute San Raffaele, Milan, Italy

10 Endocrinology Unit, Department of Experimental, Clinical and Biomedical Sciences, University of Florence, Florence, Italy

thus leading the WHO to declare the status of a pandemic condition in mid-March 2020 (https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2020/3/who-announces-covid-19-outbreak-a-pandemic). The outbreak has been putting dramatic pressure on healthcare systems worldwide resulting globally, on 1st October 2020, in 32,722,075 confirmed cases and 1,009,270 deaths (https://covid19.who.int/).

The specific mechanisms and risk factors underlying a more severe clinical manifestation and outcomes of COVID-19, rather than a milder course, are still largely unknown. However, epidemiological data have emphasized from the beginning the possibility that older age and a large number of comorbid conditions represent common markers of higher mortality and morbidity in COVID-19 [1–4]. Diabetes mellitus (DM) and poor glucose control represent crucial factors for higher risk of worse COVID-19 outcome [5–7].Available evidence indicates that, while DM does not increase the risk of contracting COVID-19, its presence is closely related to worse outcomes, particularly in poorly controlled subjects [8–10]. Several pathogenetic mechanisms, including modulation of immune response, predisposition to severe infection, associated morbidities and common use of agents able to modulate angiotensin-converting enzyme 2 (ACE2) expression, have put forth to explain the latter association [8]. However, it is important to recognize that the vast majority of the available data regarding the role of DM on SARS-CoV2 infection derives from observational studies, preventing us from adequately addressing pathogenetic inferences [11]. Similarly, the specific contribution of the other morbidities to COVID-19 mortality and morbidity is largely unknown.

Gender is another important factor to be considered in the evaluation of SARS-CoV-2 infection sequelae. In fact, despite a similar prevalence in virus infection between men and women, a well-documented, gender-related difference in terms of disease severity has been reported, with women characterized by an overall more favorable outcome, when compared to that observed in men [2, 3]. In line with this view, a recent meta-analysis, considering epidemiological data from six countries, including England, Israel, Italy, Spain and the US, showed that men had a higher risk of fatality rate, regardless of age, when compared to women [12]. The reasons for such associations are probably multifactorial and still largely unknown. Social and cultural behaviors reported in men, including higher frequency of smoking habits and alcohol intake, along with higher prevalence of comorbidities, have all been considered as possible, gender-related risk factors [13]. Furthermore, the contribution of hormones and, in particular, of testosterone (T), has been object of an intense debate in the scientific literature [13–15]. However, emerging evidence supports that low T, rather than high T, can better explain the higher risk for COVID-19 lethality observed in men [13–16]. In previous studies, low T has been associated with worse metabolic features [17–20] and with a higher risk of overall and cardiovascular (CV) mortality and morbidity in aging men [21, 22]. Hence it is possible that men with COVID-19 and low T are enriched with comorbidities, which can lead to unfavorable outcomes. It has been speculated that low T might not play a direct pathogenic role, but it could be considered just a resilient adaptation, turning off T-dependent functions (such as reproduction and/or physical and sexual activity) that are not desirable when the physical condition is ailing [23, 24].

The presence of SARS-CoV-2 was officially documented in Europe at the end of February 2020. Among others, Italy was one of the most affected countries, along with Spain, France and the UK [25]. Despite these observations, the real impact of COVID-19 in the European Union (EU), its underlying factors and their contribution to mortality and morbidity outcomes were never systematically investigated.

Available meta-analyses investigating the factors underlying COVID-19 mortality in hospitalized patients are of poor quality, mainly limited to the Chinese population and/or to the first wave ofSARS-CoV-2 infection [26–29]. Both data related to non-Chinese subjects and possible comparisons among different countries are actually poorly reported [30–34]. Using a meta-analytic method, the aim of the present study is to provide an overview of the main predictors of mean mortality rate (MR) related to SARS-CoV-2 infection in hospitalized patients, according to available published data. In addition, the contribution of the associated morbidities, age and gender to COVID-19 outcomes in the same population will be also analyzed. Finally, possible differences among countries analyzed will be investigated.

2 Methods

This meta-analysis was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline [see Supplementary file 1]. The protocol of this study (CRD42020193145) was published on the website of the University of York (Centre for Reviews and Dissemination) https://www.crd.york.ac.uk/PROSPERO.

3 Search strategy

An extensive Medline, Embase and Cochrane search was performed, including the following words: "covid"[All Fields] AND ("mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading]).

The search, which accrued data from January 1st, 2020 up to July 31, 2020, was restricted to English-language articles and studies including human participants. The identification of relevant studies was performed independently by three of the authors (W.V, A.P, G.R), and conflicts were resolved by the first investigator (G.C). All the data identified during the first analysis were checked in a second wave analysis by two of the authors (F.S, A.S). Possible further conflicts were discussed and resolved by the first investigator (G.C). We did not employ search software but hand-searched bibliographies of retrieved papers for additional references. All the authors adequately contributed to the analysis of the paper and reviewed the final version of the manuscript. The main source of information was derived from published articles.

4 Study selection

All prospective and retrospective observational studies reporting crude overall COVID-19-related MR in hospitalized subjects, without any arbitrary restriction, were included, even if mortality was not the principal endpoint (see Fig. 1 and Table 1) [1, 6, 15, 35–118]

No country restriction was applied. Data reporting mortality rate only in studies or case series of subjects not admitted to the hospital were excluded from the analysis (see Fig. 1). Studies not specifically stating the occurrence or absence of overall MR were excluded from the analysis.

5 Outcome and quality assessment

Primary outcome was the analysis of overall MR in patients admitted to the hospital due to symptomatic SARS-CoV-2 infection. Secondary outcomes included the comparison of overall MR according to age and to different countries analyzed. In addition, the effect of several risk factors including DM, hypertension, cardiovascular diseases as well as chronic kidney diseases (CKD) and chronic obstructive pulmonary diseases (COPD) on overall mortality was analyzed. Similarly, the impact of clinical symptoms and biochemical parameters on mortality at admission was investigated. The quality of trials included was assessed using the Cochrane criteria [119]. In particular, we evaluated the following criteria: the weaknesses of the designs that have been used (such as noting their potential to ascertain causality), the execution of the studies through a careful assessment of their risk of bias, especially the potential for selection bias and confounding to which all observational studies are susceptible, and the potential for reporting biases, including selective reporting of outcomes.

6 Statistical analysis

Heterogeneity in MR was assessed using I^2 statistics. Even when low heterogeneity was detected, a random-effect model was applied because the validity of tests

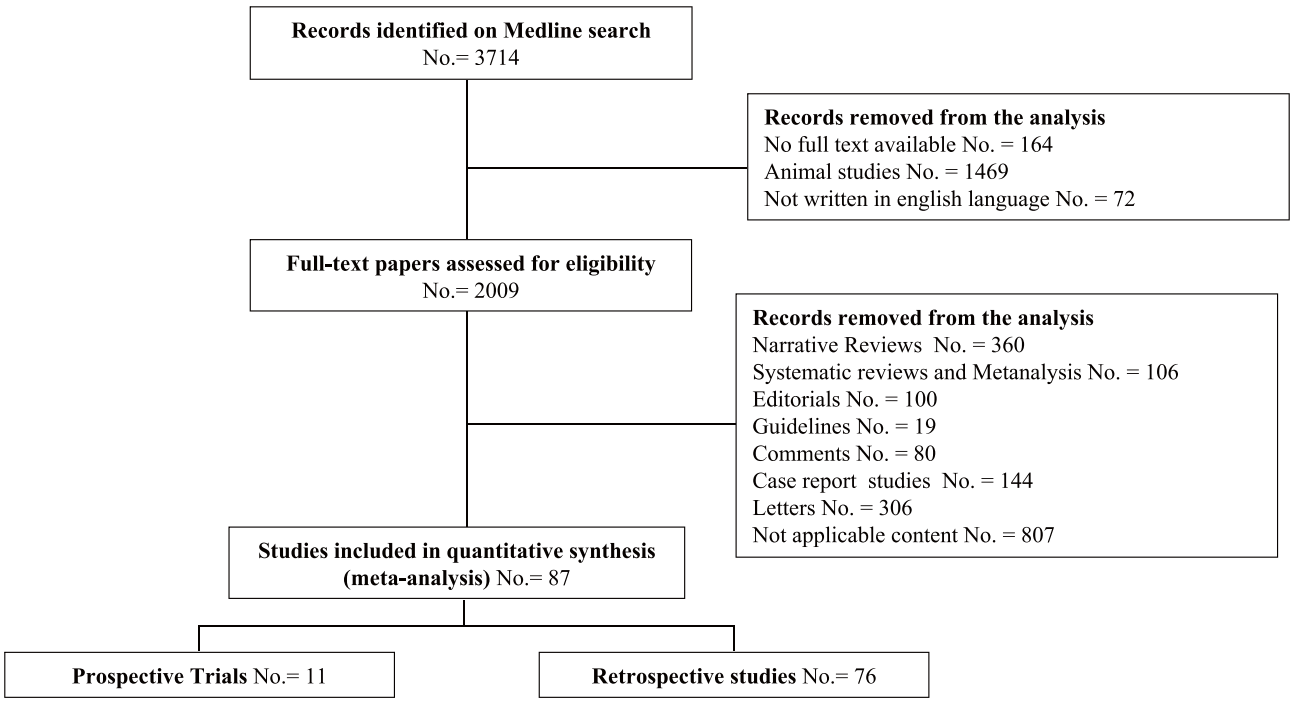

Fig. 1 Trial flow diagram for a systematic review and meta-analysis of mortality rate in hospitalized patients with COVID-19. Not applicable content = paediatric population, erratum, mortality not reported, useless clinical data, national registry, autoptic case series, histo-pathological series

Table 1 Characteristics of trials included in the meta-analysis

Authors	N° Pts	N° Deaths	Study Area	Population type	Study Design		Male (%)	Follow up (Months)	Mean age (years)
Abrishami A et al. [35]	43	5	Other (Iran)	HI	S	R	65,1	6	60,7
Aggarwal S et al. [36]	16	3	USA (IA)	HI	S	R	75	5	67
Alberici F et al. [37]	20	5	Europe (Italy)	HI	S	R	80	4	59
Argenziano GM et al. [38]	1000	211	USA (NY)	HI	S	R	60	5	63
Arshad S et al. [39]	2541	460	USA (MI)	HI	M	R	51	6	64
Bezzio C et al. [40]	79	6	Europe (Italy	HI	M	P	56	7	45
Borba MGS et al. [41]	81	22	Other (Brasil)	HI	S	P	75	4	51,1
Burns GP et al. [42]	28	14	Europe (UK)	HI	S	R	53,6	7	81,5
Campochiaro C et al. [43]	65	16	Europe (Italy)	HI, ICU	S	R	81	6	63,3
Cao B et al. [44]	199	44	Asia (China)	HI	S	P	60	3	58
Capra R et al. [45]	85	13	Europe (Italy)	HI	S	R	75	5	65
Cheng Y et al. [46]	701	113	Asia (China)	HI	S	R	52	3	63
Chilimuri S et al. [47]	375	160	USA (NY)	HI	S	R	63	7	63
Chung MS et al. [48]	110	6	Asia (South Korea)	HI, ICU	S	R	43,6	6	56,9
Cui X et al. [49]	116	24	Asia (China)	HI	M	R	56,9	7	59,2
De Smet R et al. [50]	81	19	Europe (Belgium)	HI	S	R	41	6	85
Du RH et al. [51]	179	21	Asia (China)	HI	S	P	54	3	57,6
Feng Y et al. [52]	476	38	Asia (China)	HI	M	R	57	6	53
Gao S et al. [53]	210	35	Asia (China)	HI	S	R	48	6	71
Gregoriano C et al. [54]	99	18	Europe (Switzerland)	HI, ICU	S	R	63	7	67
Grein J et al. [55]	53	7	Asia, Canada, Europe, USA§	HI	S	R	75	6	64
Hong KS et al. [56]	98	5	Asia (South Korea)	HI	S	R	39	5	55,4
Huang M et al. [57]	60	0	Asia (China)	ICU	M	R	58,3	7	57
Inciardi M et al. [58]	99	26	Europe (Italy)	HI	S	R	81	5	67
Israelsen SB et al. [59]	175	43	Europe (Denmark)	HI	S	R	49	6	71
Itelman E et al. [60]	162	5	Other (Israel)	HI	S	R	65	5	52
Jang JG et al. [61]	110	6	Asia (South Korea)	HI	S	R	43,6	6	56,9
Lagi F et al. [62]	84	8	Europe (Italy)	HI	S	R	65	5	62
Lecronier M et al. [63]	80	25	Europe (France)	ICU	S	R	80	7	57
Lewnard JA et al. [64]	1095	202	USA (CA, WA)	HI	M	P	56	5	61
Li L et al.[65]	93	25	Asia (China)	HI	S	P	44	5	51
Li R et al. [66]	225	2	Asia (China)	HI	S	R	53	6	50
Li X et al. [67]	8	4	Asia (China)	ICU	S	R	75	5	64,25
Liu X et al. [68] *	39	2	Asia (China)	ICU	S	R	64	7	64
Liu X et al., [68]**	40	9	Asia (China)	HI	S	R	63	7	61
McMichael TM et al. [69]	81	22	USA (WA)	LTC	S	R	35	3	81
Meng Y et al. [70]	168	17	Asia (China)	HI, ICU	S	R	51	4	56,7
Miyashita S et al. [71]	2071	429	USA (NY)	Mixed	S	R	43,9	7	
Moghaddam A et al. [72]	33	6	Europe (Germany)	HI	S	P	42	7	77
Morena V et al. [73]	51	14	Europe (Italy)	HI	S	P	78	5	60
Myrstad M et al. [74]	66	13	Europe (Norway)	HI	S	P	57,5	7	67,9
Na KR et al. [75]	66	0	Asia (South Korea)	HI	S	R	53	7	45,6
Nightingale R et al. [76]	24	5	Europe (UK)	HI	S	R	88		52
Nikpouraghdam M et al. [77]	2964	239	Other (Iran)	HI	S	R	66	5	55,5
Nowak B et al. [78]	169	44	Europe (Poland)	HI	S	R	51	5	63,7
Pan F et al. [79]	124	41	Asia (China)	HI	S	R	50,8		56
Pei G et al. [80]	333	29	Asia (China)	HI	S	R	55	6	56,3
Pellaud C et al. [81]	196	32	Europe (Switzerland)	HI	M	R	61	7	70
Rastrelli G et al. [15]	31	2	Europe (Italy)	HI	S	R	100	5	66,2

Table 1 (continued)

Authors	N° Pts	N° Deaths	Study Area	Population type	Study Design		Male (%)	Follow up (Months)	Mean age (years)
Ren H et al. [82]	151	33	Asia (China)	HI	S	R	52	5	59,5
Ruan Q et al. [83]	150	68	Asia (China)	HI	M	R	68,1	2	57,7
Satlin MJ et al. [84]	141	32	USA (NY)	HI	M	R	63	7	62
Senkal N et al. [85]	156	12	Europe (Turkey)	HI	S	R	53,2	7	63,7
Shao F et al. [86]	136	132	Asia (China)	HI (SHF)	S	R	66	4	69
Shi Y et al. [87]	487	0	Asia (China)	HI	M	R	53	3	46
Smith AA et al. [88]	346	117	USA (CT,MA)	HI	M	R	56,1	7	66,9
Song JW et al. [89]	41	2	Asia (China)	HI	S	P	61	7	39
Steinberg E et al. [90]	210	18	USA (NJ)	HI	2	R		7	
Tang N et a. [91]	449	134	Asia (China)	HI	S	R	60	3	65,1
Tharakan S et al. [92]	7614	1286	USA (NY)	HI	M	R	54,2	7	59,4
Trigo J et al. [93]	576	127	Europe (Spain)	HI	S	R	56,7	4	67,2
Vuagnat P et al. [94]	59	4	Europe (France)	HI	S	P	0	5	58
Wang B et al. [95]	36	14	USA (NY)	HI	S	R	63,7	7	69,8
Wang L et al. [96]	339	65	Asia (China)	HI	S	R	49	3	69
Wang L et al. [97]***	116	7	Asia (China)	HI	S	R	58	3	54
Wang Y et al. [98]	344	133	Asia (China)	ICU	S	R	52	6	64
Xie J et al. [99]	140	36	Asia (China)	HI	S	R	51	4	60
Xu J et al. [100]	239	147	Asia (China)	HI	M	R	59,8	7	62,5
Xu PP et al. [101]	703	33	Asia (China)	HI	M	R	54	5	46,1
Xu X et al. [102]	21	0	Asia (China)	HI	M	R	86	4	56,8
Yan Y et al. [103]	193	108	Asia (China)	HI	S	R	59	4	64
Yang BY et al. [104]	124	65	USA (WA)	Mixed	S	R	46,8	7	75,7
Yang Q et al. [105]	226	50	Asia (China)	HI	S	R	50	7	53,88
Yang X et al. [106]	1476	238	Asia (China)	HI	S	R	53	6	57
Ye W et al. [107]	349	36	Asia (China)	HI	S	R	49,6	7	62
Yuan M et al. [108]	27	10	Asia (China)	HI	S	R	44	3	60
Zhang G [109]	221	12	Asia (China)	HI	S	R	49	4	55
Zhang J et al. [110]	663	25	Asia (China)	HI	S	R	48	4	55,6
Zhang J et al. [111]***	108	1	Asia (China)	HI	S	R	55,6	7	66
Zhang L et al. [112]	343	13	Asia (China)	HI	S	R	49	4	62
Zhang P et al. [113]*	188	16	Asia (China)	HI	M	R	53	6	64
Zhang P et al. [113]**	940	82	Asia (China)	HI	M	R	54	6	64
Zhang S et al. [114]	828	146	Asia (China)	HI	M	R	53,9	7	62
Zhang SY et al. [115]	788	0	Asia (China)	HI, ICU	S	R	59,9	7	45,8
Zhao XY et al. [116]	91	2	Asia (China)	HI	S	R	54	4	46
Zhou F et al. [1]	191	54	Asia (China)	HI	M	R	62	3	56
Zhu L et al., [6]*	282	3	Asia (China)	HI (CDM)	M	R	48	6	62
Zhu L et al. [6]**	528	58	Asia (China)	HI (UDM)	M	R	56	6	63
Zhu L et al. [117]***	10	1	Asia (China)	HI (RT)	S	R	80	4	76
Zou X et al. [118]	154	52	Asia (China)	HI	S	R	43,5	7	60,6

§ Asia (Japan), Canada (ON), Europe (Austria, France, Germany, Italy, Netherlands, Spain), USA (CA, IL, NY, RI, WA)

HI Hospital Inpatients, *LTC* Long-Term Care, *ICU* Intensive Care Unit, *Mixed* Inpatients and Outpatients, *R* retrospective, *P* prospective, *S* single center, *M* multi-center

*same study cohort, different groups, **same study cohort, different groups, ***same name but different study

of heterogeneity can be limited with a small number of component studies. We used funnel plots and the Begg adjusted rank correlation test to estimate possible publication or disclosure bias [120]; however, undetected bias may still be present, because these tests have low statistical power when the number of trials is small. Overall

mortality is expressed as mean percentage (95% confidence interval).

In addition, a meta-regression analysis was performed to test the effect of different parameters on overall mortality. Finally, a linear regression analysis model, weighting each study for the number of subjects enrolled, was performed to verify the independent effect of specific parameters on overall mortality, after the adjustment for confounders. Following on that, potential predictors of overall mortality were included as continuous variables: associated morbidities (including hypertension, DM, COPD, cardiovascular diseases, CVD, CKD, and active malignancies), as well as clinical symptoms (including fever, cough, dyspnea and fatigue, myalgia, sore through, and gastro-intestinal symptoms) and laboratory parameters (including white, lymphocyte and platelet blood count, hemoglobin levels, C-reactive protein and D-dimer levels). All data were calculated using Comprehensive Meta-analysis Version 2, Biostat (Englewood, NJ, USA). Linear regression analysis was performed on SPSS (Statistical Package for the Social Sciences; Chicago, USA) for Windows 22.5.

7 Results

7.1 General descriptive data

Out of 3714 retrieved articles, 87 were included in the study (Table 1). Among them, 11 prospectively investigated the MR, whereas only a retrospective data analysis had been performed in the remaining 76 studies (Table 1). The study flow is summarized in Fig. 1. Among the included studies, 48 were from Asia (44 from China, and four from South Korea, respectively), 21 from Europe (eight from Italy, two from the UK, France and Switzerland, and one from Denmark, Germany, Poland, Turkey, Belgium, Spain and Norway, respectively), 13 from the US, and four from other countries (two from Iran, and one from Israel and Brazil, respectively). In addition, one study included a multicenter evaluation, including Japan, US, Canada and Europe (see Table 1). The characteristics of the retrieved trials (including parameters on trial quality) are reported in Tables 1 and 2 and in Supplementary Table 1. Retrieved trials included 35,486 patients and 5867 deaths. Mean age of population included was 60.9 ± 8.2 years, with males more prevalent than females (57.7 ± 13.5%). Finally, mean follow up was 38.4 ± 9.0 days.

The I^2 in trials assessing overall mortality was 95.3 ($p < 0.0001$). Mean crude MR was 17[15;19]% (Fig. 2). A funnel plot and Begg adjusted rank correlation test (Kendall's τ: -0.18; $p = 0.01$) suggested publication bias (Supplementary Fig. 1). However, when applying Duval and Tweedie's trim and fill method, the MR was not meaningfully affected (MR = 20[18;23]%). Both the US and European MR was higher when compared to that reported in Asia (Q = 15.73 and Q = 6.59 for US vs. Asia and for Europe vs. Asia, respectively; both $p < 0.02$). The US MR was also higher than that observed in other counties (Q = 6.25, $p < 0.02$ for US vs. others), while this comparison did not reach statistical significance for Europe (Q = 3.28; $p = 0.07$ for Europe vs. others). No difference in MR between Europe and the US was observed, although a trend toward a higher MR in the US was detected (Q = 2.91; $p = 0.08$; see also Fig. 2 and Supplementary Fig. 2 panels A-D). No significant differences in MR were observed when retrospective studies were compared to prospective ones (MR = 17[14;19]% vs. 18[14;22]%, respectively; Q = 0.30, $p = 0.58$) or when multicenter were compared to single center studies (MR = 17[15;20]% vs. 15[12;19]%; Q = 1.11 $p = 0.29$). Finally, similar data were detected in a sensitivity analysis after excluding those studies ($n = 2$, see Table 1) analyzing a mixed population of hospitalized and non-hospitalized patients (MR = 17[15;19]%) or when high quality studies were compared to low-moderate ones (MR = 14[10:17] vs. 17[15;20] respectively; Q = 3.13, $p = 0.08$).

Meta-regression analysis showed that MR was significantly higher in older subjects and in those studies enrolling a larger proportion of males (see Table 1 and Supplementary Fig. 3, panels A and B). Accordingly, the MR progressively increased as a function of age decades (Q = 15.51, 26.35, 27.19 for 50–60, 60–70 or over 70 vs. 30–40 years old; all $p < 0.0001$; see also Fig. 2). The association between MR and male gender was confirmed in a multivariate linear regression analysis, weighting each study for the number of subjects enrolled, after the adjustment for age (Adj.r = 0.175; $p < 0.0001$).

7.2 Associated morbidities

Among the associated morbidities reported, arterial hypertension was the most prevalent (mean 40.8%) followed by DM (22.3%), CVD (18.5%), CKD (12.0%), active malignancies (8.2%) and COPD (6.8%). Meta-regression analysis was applied to investigate the effect of several associated morbidities on MR. After the exclusion of those studies enrolling 100% hypertensive subjects (Table 1 and 2), hypertension was directly associated with higher MR (Fig. 3, panel A). Similar data were observed when the impact of DM, COPD, CVD, malignancies and CKD were evaluated (Fig. 3, panel B-F). In order to verify the best predictors of MR among the different associated morbidities, a series of alternative multivariate linear regression analyses were performed, weighting each study for the number of subjects enrolled and by introducing in the same model, as possible predictors of mortality, the different associated morbidities, age, trial duration and gender. Table 3 reports the results of this analysis. All the associated morbidities tested remained significantly associated with a higher MR, even after the adjustment for confounders. Among them, DM, COPD and malignancies

Table 2 Parameters reported per single trial included in the meta-analysis

Authors	Mean age (years)	HPT (%)	DM (%)	Mortality rate according to presence or absence of DM (%)	COPD (%)	Malignancy (%)	CVD (%)	CKD (%)	Duration (days)	RR (bpm)	Dyspnea (%)	Myalgia (%)	Fatigue (%)	Severe disease on admission (%)	Critical diseases on admission (%)	Linfocyte count ($\times 10^6$/ml)	PLT count ($\times 10^3$/mL)	CRP (mg/L)	D-dimer >0,5 mg/L (%)
Abrishami A et al. [35]	X	X	X	X			X	X	X	X	X	X						X	
Aggarwal S et al. [36]	X	X	X		X	X	X	X	X		X		X			X	X	X	
Alberici F et al. [37]	X	X	X				X	X	X		X	X				X	X	X	X
Argenziano GM et al. [38]	X	X	X		X	X	X	X	X		X	X			X				
Arshad S et al. [39]	X	X	X	X	X	X	X	X	X										
Bezzio C et al. [40]	X	X			X	X	X		X		X	X							
Borba MGS et al. [41]	X	X	X		X		X	X	X	X							X	X	
Burns GP et al. [42]	X	X	X		X	X	X	X	X										
Campochiaro C et al. [43]	X	X	X	X	X	X	X	X	X									X	
Cao B et al. [44]	X	X	X			X	X		X							X	X		
Capra R et al. [45]	X	X	X				X							X	X			X	
Cheng Y et al. [46]	X	X	X		X	X		2						X		X	X		X
Chilimuri S et al. [47]	X	X	X	X	X		X	X	X									X	X
Chung MS et al. [48]	X	X	X	X	X	X	X			X	X	X			X		X	X	
Cui X et al. [49]	X	X	X		X		X	X	X			X		X	X	X		X	
De Smet R et al. [50]	X								X							X		X	
Du RH et al. [51]	X	X	X	X		X	X	X	X	X	X	X	X			X		X	
Feng Y et al. [52]	X	X	X		X	X	X	X	X		X	X		X	X	X	X	X	
Gao S et al. [53]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X

Table 2 (continued)

Authors	Mean age (years)	HPT (%)	DM (%)	Mortality rate according to presence or absence of DM (%)	COPD (%)	Malignancy (%)	CVD (%)	CKD (%)	Duration (days)	RR (bpm)	Dyspnea (%)	Myalgia (%)	Fatigue (%)	Severe disease on admission (%)	Critical diseases on admission (%)	Linfocyte count ($\times 10^6$/ml)	PLT count ($\times 10^3$/mL)	CRP (mg/L)	D-dimer >0,5 mg/L (%)
Gregoriano C et al. [54]	X	X	X		X	X	X	X	X	X						X		X	
Grein J et al. [55]	X	X	X		X				X						X				
Hong KS et al. [56]	X	X	X		X	X	X			v	X	X			X			X	
Huang M et al. [57]	X	X	X		X		X	X	X		X	X	X						
Inciardi M et al. [58]	X	X	X		X	X	X	X	X							X	X	X	
Israelsen SB et al. [59]	X	X	X		X		X		X		X	X	X			X	X	X	
Itelman E et al. [60]	X	X	X		X		X	X	X					X		X	X	X	
Jang JG et al. [61]	X	X	X		X	X	X		X	X					X				
Lagi F et al. [62]	X	X	X		X	X	X	X	X			X			X	X	X	X	
Lecronier M et al. [63]	X	X	X		X		X		X	X					X	X			
Lewnard JA et al. [64]	X								X										
Li L et al. [65]	X	X	X	X	X	X	X		X		X	X	X			X	X	X	
Li R et al. [66]	X	X							X		X								
Li X et al. [67]	X	X	X		X	X	X	X	X										
Liu X et al. [68] *	X	X	X		X		X	X	X		X	X	X	X	X	X	X	X	
Liu X et al., [68]**	X	X	X		X		X	X	X		X	X	X	X	X	X	X	X	X
McMichael TM et al. [69]	X	X	X		X	X	X	X	X										
Meng Y et al. [70]	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X

Table 2 (continued)

Authors	Mean age (years)	HPT (%)	DM (%)	Mortality rate according to presence or absence of DM (%)	COPD (%)	Malignancy (%)	CVD (%)	CKD (%)	Duration (days)	RR (bpm)	Dyspnea (%)	Myalgia (%)	Fatigue (%)	Severe disease on admission (%)	Critical diseases on admission (%)	Linfocyte count ($\times 10^6$/ml)	PLT count ($\times 10^3$/mL)	CRP (mg/L)	D-dimer >0,5 mg/L (%)
Miyashita S et al. [71]		X	X					X	X					X	X				
Moghaddam A et al. [72]	X	X	X		X		X												
Morena V et al. [73]	X	X	X		X	X	X		X		X			X	X	X	X	X	X
Myrstad M et al. [74]	X	X	X		X	X	X	X	X	X	X							0	
Na KR et al. [75]	X	X	X				X		X										
Nightingale R et al. [76]	X	X	X				X		X										
Nikpour-aghdam M et al. [7]	X	X	X		X	X	X		X										
Nowak B et al. [78]	X	X	X		X	X	X	X	X		X								
Pan F et al. [79]	X	X	X	X			X		X			X				X	X	X	
Pei G et al. [80]	X	X	X						X		X			X	X	X		X	X
Pellaud C et al. [81]	X	X	X		X	X	X		X										
Rastrelli G et al. [15]	X	X	X				X	X								X	X	X	
Ren H et al. [82]	X	X	X		X		X	X	X	X	X		X	X		X		X	
Ruan Q et al. [83]	X	X	X	X	X	X	X	X			X	X	X			X	X	X	
Satlin MJ et al. [84]	X	X	X		X	X	X	X	X		X	X		X		X	X		
Senkal N et al. [85]	X	X	X		X		X		X	X						X		X	
Shao F et al. [86]	X	X	X		X	X	X	X	X		X	X	X		X				
Shi Y et al. [87]	X	X	X			X	X	X						X					

Table 2 (continued)

Authors	Mean age (years)	HPT (%)	DM (%)	Mortality rate according to presence or absence of DM (%)	COPD (%)	Malignancy (%)	CVD (%)	CKD (%)	Duration (days)	RR (bpm)	Dyspnea (%)	Myalgia (%)	Fatigue (%)	Severe disease on admission (%)	Critical diseases on admission (%)	Linfocyte count ($\times 10^6$/ml)	PLT count ($\times 10^3$/mL)	CRP (mg/L)	D-dimer >0,5 mg/L (%)
Smith AA et al. [88]	X	X	X	X	X	X	X	X	X										
Song JW et al. [89]	X	X	X			X					X	X				X	X	X	
Steinberg E et al. [90]									X										
Tang N et a. [91]	X								X										X
Tharakan S et al. [92]	X																		
Trigo J et al. [93]	X	X	X		X		X		X		X	X	X			X	X	X	X
Vuagnat P et al. [94]	X	X	X		X	X	X		X		X				X	X			
Wang B et al. [95]	X	X	X	X	X	X	X	X	X							X			
Wang L et al. [96]	X	X	X		X	X	X	X	X	X	X	X	X			X	X	X	X
Wang L et al. [97]***	X	X	X			X	X	X	X					X					
Wang Y et al. [98]	X	X	X	X	X		X		X	X	X		X			X	X	X	X
Xie J et al. [99]	X	X	X		X	X	X	X	X		X			X	X	X	X	X	
Xu J et al. [100]	X	X	X	X	X	X	X		X							X	X		
Xu PP et al. [101]	X	X	X	X	X	X	X	X	X		X	X	X	X	X			X	X
Xu X et al. [102]	X	X	X		X		X	X	X				X	X	X		X	X	
Yan Y et al. [103]	X	X	X		X		X	X	X		X		X	X		X	X	X	
Yang BY et al. [104]	X	X	X		X	X	X	X	X		X	X	X		X				
Yang Q et al. [105]	X	X	X	X	X		X		X							X			
Yang X et al. [106]	X																		

Table 2 (continued)

Authors	Mean age (years)	HPT (%)	DM (%)	Mortality rate according to presence or absence of DM (%)	COPD (%)	Malignancy (%)	CVD (%)	CKD (%)	Duration (days)	RR (bpm)	Dyspnea (%)	Myalgia (%)	Fatigue (%)	Severe disease on admission (%)	Critical diseases on admission (%)	Linfocyte count ($\times 10^6$/ml)	PLT count ($\times 10^3$/mL)	CRP (mg/L)	D-dimer >0,5 mg/L (%)
Ye W et al. [107]	X	X	X	X					X									X	
Yuan M et al. [108]	X	X	X	X		X		X		X	X				X				
Zhang G [109]	X	X	X		X	X	X	X	X	X	X		X	X		X	X		
Zhang J et al. [110]	X				X	X	X	X	X	X	X	X	X	X	X				
Zhang J et al. [111]***	X	X	X		X	X	X	X	X	X	X	X	X			X	X	X	
Zhang L et al. [112]	X	X	X		X	X	X	X	X							X	X	X	X
Zhang P et al. [113]	X	X	X		X		X	X	X	X	X		X						X
Zhang P et al. [113]*	X	X	X		X		X	X	X	X	X		X						X
Zhang S et al. [114]	X	X	X		X	X	X	X	X		X	X	X	X		X	X	X	
Zhang SY et al. [115]	X	X	X		X		X	X	X			X	X	X	X	X	X	X	
Zhao XY et al. [116]	X	X	X		X	X		X	X			X	X	X					
Zhou F et al. [1]	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X		X
Zhu L et al., [6]	X	X	X		X		X	X	X	X	X		X						X
Zhu L et al. [6]*	X	X	X		X		X	X	X	X	X		X						X
Zhu L et al. [117]***	X							X					X	X	X				
Zou X et al. [118]	X	X	X		X	X	X		X	X	X								

DM Diabetes Mellitus, *CDM* controlled diabetes mellitus, *UDM* uncontrolled diabetes mellitus, *SHF* sudden heart failure, *RT* Renal Transplantation,
*same study cohort, different groups; **same study cohort, different groups; ***similar name but different study

were the strongest predictors of mortality. Interestingly, when all associated morbidities were considered in the same model with sex, along with age and study duration, as possible predictors of MR, male gender retained a high statistical significance (adj.r = 0.546; p < 0.0001).

7.3 Diabetes and mortality outcomes

Since DM was the best predictor of COVID-19 related mortality, we performed a specific sub-analysis, comparing the mortality rate in patients with or without DM. Among the available studies, 20 reported mortality rate according to the presence or absence of DM (Table 2). Overall, DM was associated with a significant increased risk of mortality, when compared to that observed in the non diabetic population (Fig. 4). Interestingly, by performing a meta-regression analysis we found that the DM-increased mortality was not related to gender and attenuated in older patients (Supplementary Fig. 4, panel A -B). In addition, when the influence of other associated morbidities was analyzed, the DM-related increased mortality was reduced in those studies reporting a higher proportion of patients with arterial hypertension or CKD (Supplementary Fig. 4, panel C-D). The latter results were confirmed even after the adjustment for age (adj.r = -0.346 and -0.278 for arterial hypertension and CKD, respectively; both $p < 0.0001$). Conversely, no relationship with a previous history of CVD or COPD was observed (not shown).

7.4 Clinical symptoms at first evaluation

At first evaluation, a mean of 44.4% and 25.9% of the patients were defined as being in severe or critical condition, respectively. MR significantly increased as a function of the prevalence of subjects referred to hospital in severe or critical clinical condition (Supplementary Fig. 5, Panels A and B). The most common clinical symptoms reported were fever (73.5%), cough (64.9%), fatigue (41.3%), dyspnea (41.1%), myalgia (20.2%), diarrhea (17.2%), nausea or vomiting (11.1%) and sore throat (9.6%). In particular, among the clinical symptoms reported, meta-regression analysis showed that MR was directly related to subjective dyspnea and fatigue (Supplementary Fig. 5, Panel C and D), as well to respiratory rate (Supplementary Fig. 5, Panel E). In addition, a trend towards a significant direct association with myalgia was also observed (Supplementary Fig. 5, Panel F). Conversely, no association between a higher MR and other symptoms such as fever, cough, sore throat or gastro-intestinal problems (including diarrhea, nausea or vomiting) was observed (not shown). No sufficient data were available to test the impact of anosmia, dysgeusia or conjunctival congestions (not shown). The association between MR and the aforementioned clinical symptoms was confirmed in a multivariate linear regression analysis, weighting each study for the number of subjects enrolled and by introducing, in the same model, clinical symptoms and the aforementioned

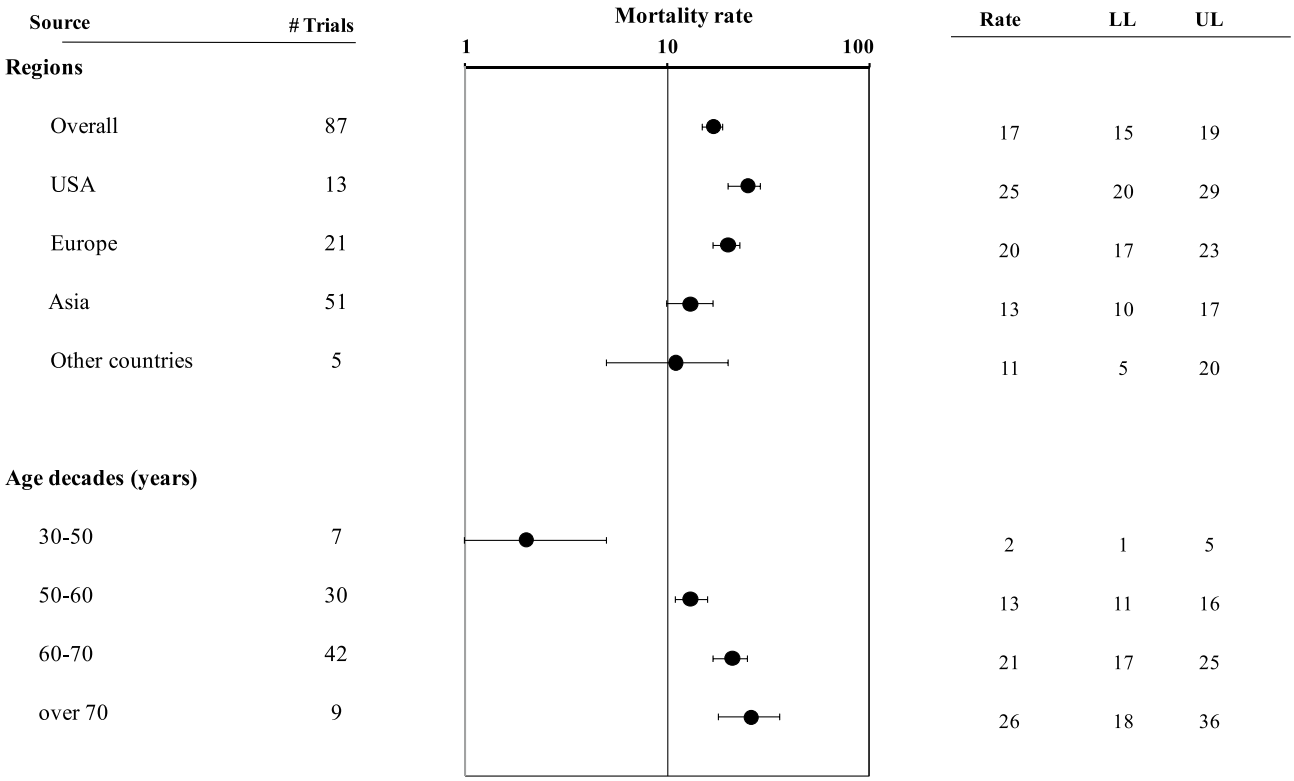

Fig. 2 Mortality rate in the whole population, in different geographical areas and as a function of age decades. LL lower levels, UP upper levels

confounders as possible predictors of differences in MR. The results of this analysis are reported in Table 3. All the symptoms were significantly and directly associated with a higher MR, even after the adjustment for confounders. At first evaluation, respiratory rate was the best predictor of MR (Table 3).

When the impact of the same symptoms was investigated, using meta-regression analysis, analyzing those studies reporting data as a function of DM, only the presence of a higher proportion of dyspnea was inversely related to DM-mortality rate (Supplementary Fig. 4, panel E; adj.r = -0.146; $p < 0.0001$ after the adjustment for age).

7.5 Laboratory findings

Among the different biochemical parameters evaluated, an inverse relationship between lymphocyte and platelet count and MR was observed (Fig. 5, Panel A and B). In addition, a positive association with C-reactive protein and elevated D-Dimer levels (i.e. > 0.5 mg/L) were also observed (Fig. 5, Panel C and D). No association between MR and white blood count and hemoglobin levels was detected (not shown). Finally, no sufficient data were available to investigate the effect of IL-6 and Troponin I levels on MR. The associations between higher MR, reduced lymphocyte and platelet count and elevated D-Dimer levels were confirmed even after the adjustment for confounders (Table 3). Conversely, the relationship between C-reactive protein and MR was not confirmed (not shown).

When the impact of the same parameters was evaluated, using meta-regression analysis, analysing those studies reporting data as a function of DM, lymphocyte count was inversely related to DM-mortality rate (Supplementary

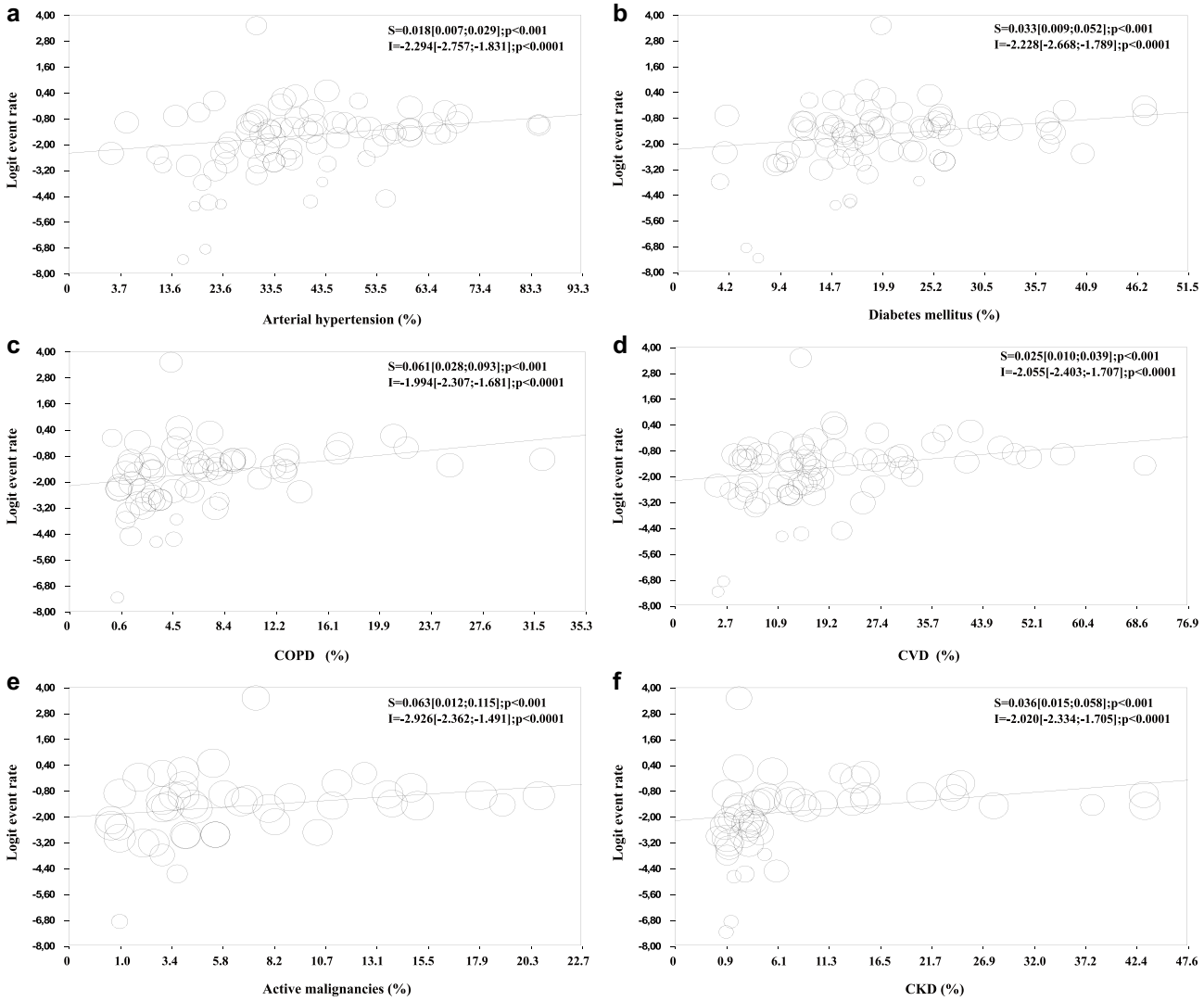

Fig. 3 Mortality rate according to different associated morbidities: arterial hypertension **a**, diabetes mellitus **b**, chronic obstructive pulmonary diseases (COPD; **c**), cardiovascular diseases (CVD; **d**), active malignancies **e**, and chronic kidney diseases (CKD; **f**)

Table 3 Adjusted relationship between end-pony mortality rate,associated morbidities, clinical symptoms and laboratory findings. Data are derived from a multivariate linear regression model, weighting each study for the number of subjects enrolled, introducing associated morbidities, age study duration and sex as possible predictors of mortality rate

		Mortality rate
	Adj r	*p*
Associated morbidities		
Arterial hypertension	0.059	0.0001
Diabetes mellitus	0.187	0.0001
COPD	0.138	0.0001
Malignancies	0.139	0.0001
CVD	0.068	0.0001
CKD	0.072	0.0001
Clinical symptoms		
Dsypnea	0.476	0.0001
Respiratory rate	0.644	0.0001
Fatigue	0.289	0.0001
Myalgia	0.439	0.0001
Laboratory parameters		
Limphocyte count	-0.504	0.0001
Platelet count	-0.492	0.0001
Elevated D-Dimer (> 0.5 mg/l)	1.076	0.0001

Fig. 4, panel F; adj.r = 0.161; $p < 0.0001$ after the adjustment for age).

8 Discussion

Applying a meta-analytic approach, we systematically reviewed and analyzed all predisposing clinical and biochemical features contributing to COVID-19-associated mortality. Our data show that associated morbidities are tightly related to an increased mortality in an age- and gender-dependent manner. Among clinical symptoms, dyspnea, fatigue and myalgia, along with respiratory rate, were the best predictors of MR, even after the adjustment for confounding factors. Finally, reduced lymphocyte and platelet count, along with increased D-dimer levels, all contribute to an overall increased mortality.

A large body of evidence has clearly documented that associated morbidities represented the most important factors related to higher MR in SARS-CoV-2 infected subjects [121]. Our data indicate that, after adjusting for confounders, DM is the best predictor of a worse COVID-19-related outcome. Interestingly, despite what observed in the whole population, the increased DM-related MR was independent to gender and attenuated in older patients. A previous meta-analysis including 6452 patients from 30 studies showed that DM was associated with a two-fold increased risk of poor outcome and mortality on COVID-19 subjects [122]. Similar data were more recently reported in a meta-analysis including 15 studies with SARS-CoV2 infection [123]. In line with these data, the Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) study—a nationwide French multicenter, observational study, aimed at identifying the clinical and biological features associated with COVID-19 outcomes in DM subjects—reported that hyperglycemia at admission worsened patient prognosis [124]. Similar observations have been previously reported for Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome SARS [125] and MERS [126]. The specific underlying mechanisms related to the increased mortality rate observed in DM-SARS-CoV2 infected subjects are far to be elucidated. Several factors related to DM have been considered. People with diabetes are characterized by pulmonary dysfunction due to decreased lung volume, reduced pulmonary diffusing capacity, as well as ventilation control, bronchomotor tone and noradrenergic innervation impairment [127]. In addition, the diabetic population is more susceptible to infection, due to the associated lymphopenia and to the exaggerated inflammatory response associated with an increased renin-angiotensin system (RAS) activation in several tissues [128]. Finally, the increased CV risk associated with DM, as well as with hypertension, can further contribute to a poor COVID-19 prognosis. A large population-based study including 264,390 subjects with type 1 DM and 2,874,020 patients with type 2 DM registered with a general practice in England showed that DM COVID-19-related mortality was higher in males and directly associated with age, CV and renal complications as well as with poorer glycemic control and higher BMI [10]. Data derived from the present meta-analysis are in line with the latter findings. Older age and larger proportion of associated morbidities such as arterial hypertension and CKD within the whole population studied attenuated the DM-related risk. In addition, the inverse relationship with dyspnea severity at hospital admission suggests that DM plays a major role in worsening milder forms of COVID-19, whereas its contribution is less evident in more severe cases. Accordingly, the DM-related mortality risk is higher in those studies including patients with a higher lymphocyte count. Information on the role of DM treatment at enrolment or during hospitalization were not available in the present meta-analysis. However, it is important to recognize that both the glycometabolic control and the type of drug used for DM treatment have been considered as crucial factors related to DM outcome in COVID-19 [129–131]. The DM-related impaired immunological function is another factor can be considered. However, Lampasona et al. [132], using a highly specific and sensitive measurement of antibody immunoassays, reported a normal humoral response against SARS-CoV2 in DM subjects with COVID-19.

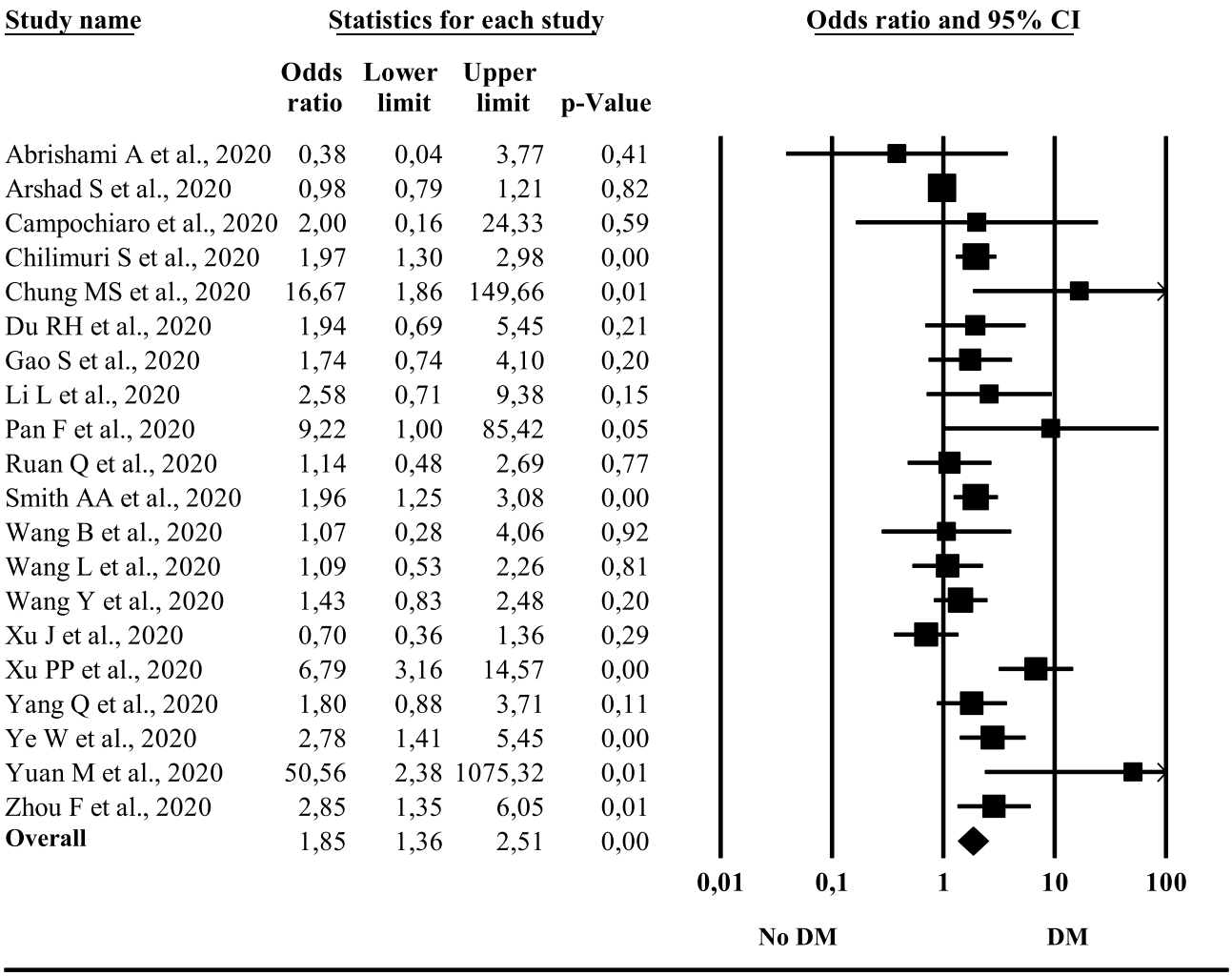

Fig. 4 Diabetes mellitus (DM)-related mortality rate. LL lower levels, UP upper levels

COPD was another independent risk factor associated with an increased mortality risk. A previous meta-analysis from China, considering only 11 case-series and 2002 subjects, showed that COPD was associated with a four-fold increased risk of mortality [133]. COPD is a chronic inflammatory condition of the large and, in particular, of the small airways, tightly related to smoking, characterized by lung parenchyma destruction, due to emphysema development and expiratory airflow limitation. The clinical presentation of COVID-19 infection can overlap with an acute exacerbation of COPD, resulting in a delay of correct clinical diagnosis and in a possible inappropriate medical intervention [121, 133]. Accordingly, a tight association between a higher MR and pulmonary symptoms, such as dyspnea and respiratory rate, was observed in the present study. All these factors can explain, at least partially, the worse outcomes observed in COPD patients.

Hypertension has been frequently reported as the most common associated morbidity in patients with COVID-19 [121].In addition, in line with what has been reported for other coronavirus infections—such as SARS and MERS—hypertension has been considered as an independent risk factor for higher mortality and morbidity in patients with SARS-CoV-2 infection [121]. The specific underlying mechanisms linking hypertension and worse COVID-19 outcomes are far from having been elucidated. A mice model showed that SARS-CoV inoculation resulted in a down regulation of ACE2 cell expression [134]. The latter in turn can cause an excessive activation of RAS, possibly contributing to COVID-19-related lung injury progression, favoring an inflammatory response and a cytokine storm, stimulating the NADH/NADPH oxidase system [134]. In this context, the use of ACE inhibitors (ACEi) or of angiotensin II receptor blockers (ARBs) might be beneficial

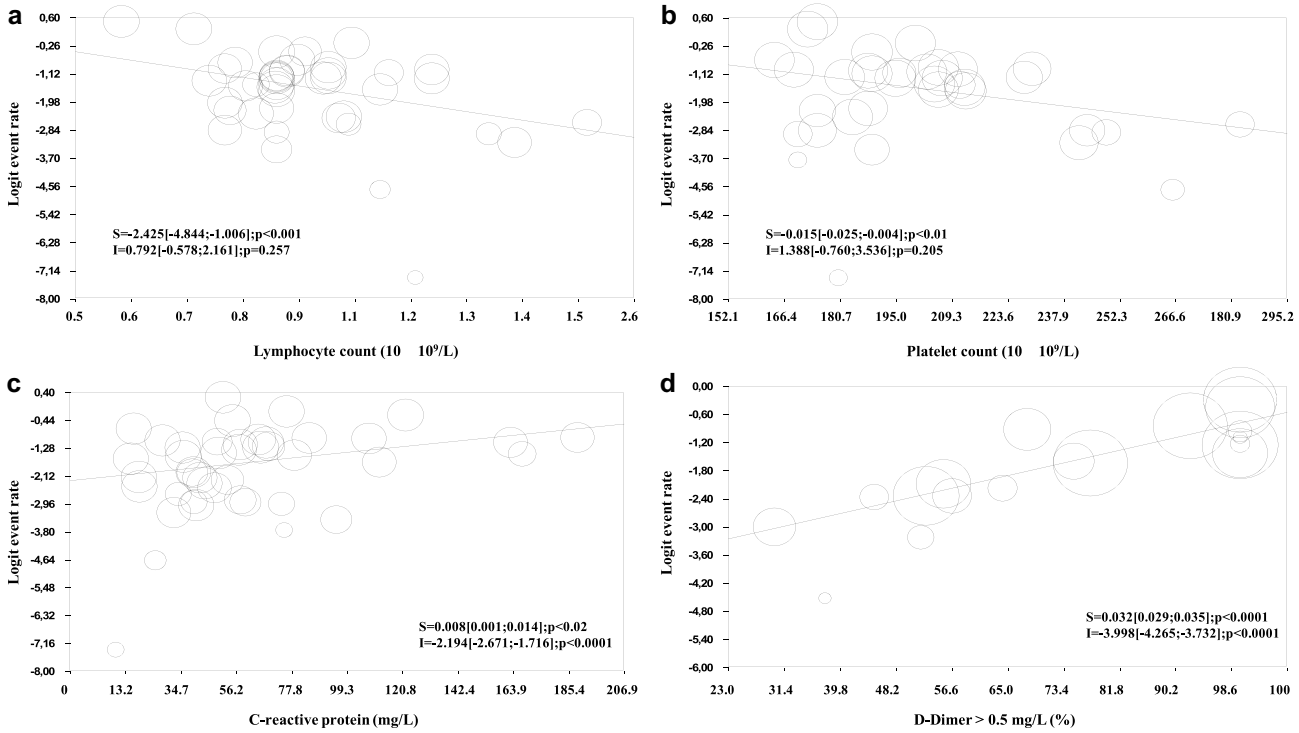

Fig. 5 Mortality rate according to different biochemical parameters: lymphocyte **a** or platelet **b** count, C-reactive protein **c**, pathological (> 0.5 mg/L) D-dimer levels **d**

for COVID-19 outcomes [25, 85]. Although conflicting results were available on this issue [135, 136], a recent meta-analysis further supports a beneficial effect of ACEi and ARBs on disease progression [137].

Patients with active malignancies [138] and CKD [139] constitute a population enriched with frail people; hence, their association with a poor COVID-19 outcome is not surprising.

The association between male sex and higher MR deserves a more critical analysis. When compared to females, males are usually characterized by a higher prevalence of associated morbidities and higher CV risk, frequently related to risky behaviors, such as smoking, alcohol consumption, a diet enriched with fat and protein and reduced physical activity [140]. In addition, when compared to women, men generally consult health care services less frequently for preventive care [141]. This can result in symptom progression and a delay in a correct diagnosis, all factors which can contribute to a higher COVID-19 mortality. Another working hypothesis deals with the possibility that a different hormonal balance can contribute to the higher MR observed in men [13]. Accordingly, T can modulate transcriptionally or post-translationally the cell expression of ACE2 receptor and TMPRSS2, both crucial for SARS-CoV-2 cell internalization [13]. In addition, genotyping analysis has documented that a specific genetic variant in TMPRSS2 gene is totally absent in the East Asian population and more frequently observed in European and African American subjects [142, 143]. In particular, this variant deals with different single nucleotide polymorphisms (SNPs) tightly associated with an androgen-dependent upregulation of TMPRSS2 expression [142, 143]. This observation can explain, at least partially, the lower MR observed in Asian populations. However, in preliminary studies, low T, more than high T, is associated with a higher COVID-19 lethality observed in men [13, 15, 16]. Accordingly, in a mouse model of influenza A virus lung infection, high androgens were associated with a more favorable pulmonary environment, promoting downregulation of detrimental inflammatory immune responses to protect against prolonged influenza disease [144]. Finally, low T is often associated with metabolic and cardiovascular derangements that could facilitate COVID-19 lethality [23, 24, 145]. Accordingly, a large placebo controlled trial showed that testosterone treatment in hypogonadal patients with impaired glucose tolerance of newly diagnosed type 2 DM (T2DM) reduced the proportion of diabetes at two years of follow up, beyond the effects of a lifestyle program [146]. Hence, variation in androgen milieu cannot completely explain the observed gender-related difference in MR. It is interesting to note that the positive relationship between male sex and lethality retains significance even after adjustment for associated comorbidities. In line with the latter hypothesis, gender was not related to DM-increased risk of mortality in the present meta-analysis.

An original finding of this study is the evaluation of the impact of clinical laboratory parameters on overall MR. Our study showed that reduced lymphocyte and platelet count, along

with increased D-dimer levels, were the best predictors of an overall increased mortality. Among the latter factors, D-dimer is the best predictor of overall mortality. Emerging evidence has documented that, besides deep venous thrombosis (DVT), elevated D-dimer in COVID-19 patients can be the expression of capillary microthrombi, due to pulmonary capillary endothelial injury, which can contribute to the increased risk of death [147]. A recent study, performed in 184 COVID-19 patients, concluded that pulmonary embolism (PE) was the most frequent thrombotic complication (81%) and that both age and coagulopathy were independent predictors of thrombotic complications [148]. Similar results were reported by other authors [149]. In line with the latter findings, a multicenter randomized controlled trial, comparing efficacy and safety of high- versus low-molecular weight heparin dosages in hospitalized patients with severe COVID-19 pneumonia and coagulopathy, is ongoing [150]. Reduced platelet count and lymphopenia, along with eosinopenia, have all been associated in these patients with more severe pneumonia and with higher inflammatory response [111]; hence, their association with higher mortality is not surprising. Similarly, symptoms such as myalgia and fatigue can be considered the expression of a more severe systemic inflammatory involvement, explaining their association with higher mortality risk.

Several limitations should be recognized. The vast majority of the meta-analyzed data derive from retrospective case series of hospitalized patients. Much evidence has clearly documented that in observational studies the completeness of follow-up and the management of missing data is crucial and a possible source of potential bias. Accordingly, a higher heterogeneity and publication bias was documented in the current study. A further limitation deals with the fact that estimating reproduction numbers for SARS-CoV-2 presents challenges due to the high proportion of infections not correctly detected by health systems, due to paucity, or even the lack, of symptoms and to changes in testing policies, thus resulting in different proportions of infections being detected over time and between countries. Hence, the reproducibility of our data warrants caution. In addition, the worldwide course of COVID-19 presents important temporal differences in line with the SARS-CoV-2 infection diffusion [151]. Hence, comparing data from different countries can constitute a further risk of bias. Finally, data on glycometabolic control and glucose variability, as well as the impact of diabetic treatment on COVID-19 outcomes, are limited, thus preventing definitive conclusions.

In conclusion, associated morbidities, and mostly diabetes mellitus, play a crucial role in COVID-19 hospitalized patient mortality. Specific biochemical parameters such as reduced lymphocyte and platelet count, as well as increased D-Dimer levels, represent other important risk factors. All physicians dealing with SARS-CoV-2 infected subjects should be aware of the underlying risk factor for poor prognosis. The optimization of glucose profile along with an adequate thrombotic complications preventive strategy must be become routine practice along with respiratory support and specific treatment, particularly in men. The specific reasons supporting the observed increased mortality in men have yet to be fully elucidated.

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Data Availability The complete dataset used for statistical analysis will be available to the Editorial Office, uploaded as Supplementary Material to the present Manuscript file.Declarations.

Declarations

Conflict of interest All authors declare that they don't have any financial interest neither they received support from institutions or companies mentioned in the present manuscript.

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