Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original research article

INR and COVID-19 severity and mortality: A systematic review with meta-analysis and meta-regression

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ABSTRACT

Objectives: D-dimer elevations, suggesting a pro-thrombotic state and coagulopathy, predict adverse outcomes in coronavirus disease 2019 (COVID-19). However, the clinical significance of other coagulation markers, particularly the international normalized ratio (INR), is not well established. We conducted a systematic review and meta-analysis of the INR in COVID-19.

Methods: A literature search was conducted in PubMed, Web of Science and Scopus, between January 2020 and February 2021, for studies reporting INR values, measures of COVID-19 severity, and mortality (PROSPERO registration number: CRD42021241468).

Results: Thirty-eight studies in 7440 COVID-19 patients with low disease severity or survivor status during follow up (50 % males, mean age 57 years) and 2331 with high severity or non-survivor status (60 % males, mean age 69 years) were identified. The INR was significantly prolonged in patients with severe disease or non-survivor status than in patients with mild disease or survivor status (standard mean difference, SMD, 0.60; 95 % confidence interval, CI 0.42 to 0.77; $p < 0.001$). There was extreme between-study heterogeneity ($I^2 = 90.2$ %; $p < 0.001$). Sensitivity analysis, performed by sequentially removing each study and re-assessing the pooled estimates, showed that the magnitude and direction of the effect size was not modified. The Begg's and Egger's t-tests did not show publication bias. In meta-regression, the SMD of the INR was significantly associated with C-reactive protein ($p = 0.048$) and D-dimer ($p = 0.001$).

Conclusions: Prolonged INR values were significantly associated with COVID-19 severity and mortality. Both INR prolongation and D-dimer elevations can be useful in diagnosing COVID-19-associated coagulopathy and predicting clinical outcomes.

1. Introduction

Coronavirus disease 2019 (COVID-19) is frequently characterized by the presence of significant coagulopathy, particularly in the setting of a systemic release of pro-inflammatory and pro-oxidant cytokines and multi-organ compromise [1]. The COVID-19-associated coagulopathy typically involves the combined activation of coagulation, immune, and complement pathways and endothelial dysfunction [2,3]. This process results in the formation of thrombi both in the large vessels and in the microvasculature of the lungs and other organs, resembling disseminated intravascular coagulation (DIC) [2,4]. In terms of specific coagulation parameters, the most frequently observed alteration in patients with COVID-19 involves the elevation in the concentrations of D-dimer, one of the major fibrin degradation products that is released during the cleavage of crosslinked fibrin by plasmin and indicates the presence of recent or ongoing DIC and fibrinolysis [5]. Notably, D-dimer elevations in COVID-19 patients are also associated with severe forms of the disease and higher mortality [6]. While other coagulation markers are routinely tested in hospitalized COVID-19 patients, their exact pathophysiological role and clinical significance in this population are not well established. In particular, the pro-thrombin time (PT) and the international normalized ratio (INR), calculated by dividing the PT of an individual patient by that of a laboratory standard, are measured to assess both the extrinsic and the common coagulation pathways and can theoretically assist in the

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diagnosis of COVID-19-associated coagulopathy as well as the evaluation of the synthetic function of the liver [7]. However, the magnitude of the prolongation of the INR in COVID-19 patients with severe disease and coagulopathy is considered to be less prominent, and possibly less clinically significant, when compared to the D-dimer [8]. Pending further studies addressing this issue, and in the absence of a comprehensive critical appraisal of the evidence regarding the pathophysiological and prognostic role of the INR in COVID-19, we conducted a systematic review and meta-analysis of published studies reporting INR values, measures of COVID-19 severity and mortality. We hypothesized that COVID-19 patients with severe forms of the disease and/or not surviving during follow-up had a prolonged PT, and hence INR, when compared to patients with less severe forms of the disease or favorable outcomes, further supporting the presence of significant coagulopathy and a systemic pro-thrombotic state in the former. A meta-regression analysis was also conducted to identify associations between the INR effect size and several pre-defined biologically and clinically plausible parameters.

2. Materials and methods

2.1. Search strategy and study selection

A systematic literature search, using the terms "international normalized ratio" or "INR" and "coronavirus disease 19" or "COVID-19", was conducted in the electronic databases of PubMed, Web of Science, and Scopus, from January 2020 to February 2021, to identify peer-reviewed studies reporting the INR in COVID-19 patients (PROSPERO registration number: CRD42021241468). The references of the retrieved articles were also reviewed to identify additional studies. Inclusion criteria were as follows: reporting continuous INR values in COVID-19 patients, investigating COVID-19 patients with different degrees of disease severity or survival status, adult patients, English language, $\geq$10 participants, and full-text available. Abstracts were independently screened by two investigators (AZ and PP). If relevant, the full articles were reviewed. The quality of individual studies was assessed using the Newcastle-Ottawa scale, with a score $\geq$6 indicating high quality [9].

2.2. Statistical analysis

Standardized mean differences (SMDs) and 95 % confidence intervals (CIs) were calculated to build forest plots of continuous data and evaluate differences in the values of INR between COVID-19 patients with low vs. high disease severity or survivor vs. non-survivor status. If necessary, the mean and standard deviation values were extrapolated from the corresponding median and interquartile range (IQR) values [10]. The Q-statistic was used to test the between-study heterogeneity of the SMD (significance level set at $p < 0.10$). Inconsistency across studies was evaluated using the I^2 statistic: I^2<25 %, no heterogeneity; I^2 between 25 % and 50 %, moderate heterogeneity; I^2 between 50 % and 75 %, large heterogeneity; and I^2>75 %, extreme heterogeneity [11,12]. A random-effects model was used to calculate the pooled SMD and corresponding 95 % CIs in the presence of significant heterogeneity. Sensitivity analyses were conducted to evaluate the impact of individual studies on the overall effect size with the leave-one-out method [13]. The presence of publication bias was assessed with the Begg's adjusted rank correlation test and the Egger's regression asymmetry test [14,15]. The "trim-and-fill" procedure by Duval and Tweedie was also used to assess publication bias. This method recalculates a pooled SMD by incorporating the hypothetical missing studies as though they existed, to augment the observed data so that the funnel plot is more symmetric [16]. To explore possible contributors to the between-study variance, we investigated in meta-regression analysis the associations between the SMD and the following parameters: age, gender, study endpoint, study design (retrospective or prospective), geographical area where the study was conducted, liver function (aspartate aminotransferase, AST, alanine aminotransferase, ALT, albumin), coagulation markers (D-dimer, activated partial thromboplastin time, aPTT, fibrinogen), renal function (serum creatinine, urea), myocardial damage (troponin), tissue damage and sepsis (creatine kinase, CK, lactate dehydrogenase, LDH, procalcitonin), inflammation (C-reactive protein, CRP, white blood cell count, WBC, neutrophils, lymphocytes), glucose, diabetes, hypertension and cardiovascular disease. A p-value <0.05 was considered statistically significant. Analyses were performed using Stata 14 (STATA Corp., College Station, TX, USA). Our study was fully compliant with the PRISMA statement [17].

3. Results

3.1. Literature search and study selection

A flow chart of the screening process is described in Fig. 1. A total of 828 studies were initially identified. From them, 782 were excluded after the first screening because they were either duplicates or irrelevant. After a full-text review of the remaining 46 studies, 8 were further excluded because they failed to meet the inclusion criteria. Thus, 38 studies were included in the final meta-analysis (Table 1) [18–55]. A total of 9771 COVID-19 patients were investigated, 7440 (50 % males, mean age 57 years) with low disease severity or survivor status and 2331 (60 % males, mean age 69 years) with high severity or non-survivor status during follow-up.

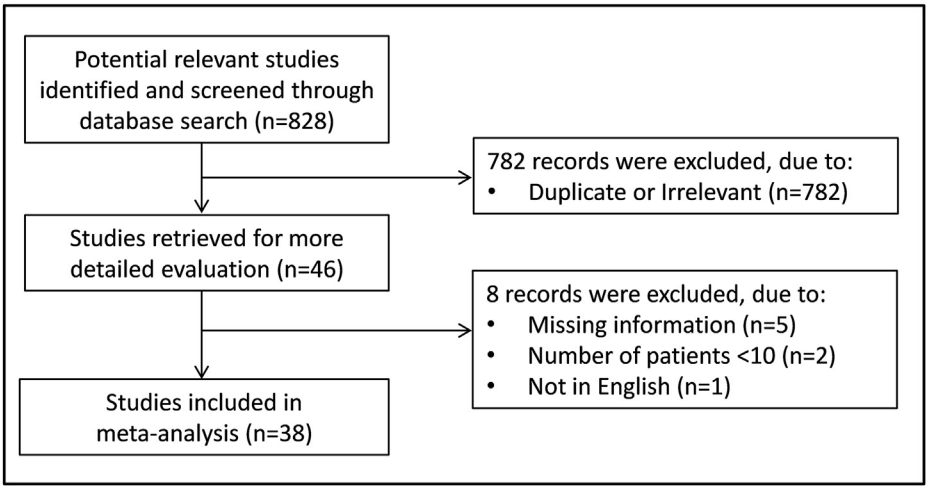

Fig. 1. Flow chart of study selection.

Table 1
Characteristics of the studies included in the meta-analysis.

				Mild disease or survivor				Severe disease or non-survivor			
First Author, Country [Ref]	**Study design**	**Endpoint**	**NOS** (stars)	**n**	**Age** (Years)	**Gender** (M/F)	**INR** (Mean ± SD)	**n**	**Age** (Years)	**Gender** (M/F)	**INR** (Mean ± SD)
Aladağ N et al., Turkey [18]	R	Survival	7	35	68	22/13	1.17 ± 0.22	15	68	6/9	1.14 ± 0.24
Altschul DJ et al., USA [19]	R	Survival	7	1733	63	771/962	1.10 ± 0.15	621	73	327/294	1.15 ± 0.15
Bao C et al., China [20]	P	Disease severity	5	129	NR	NR	1.07 ± 0.09	49	NR	NR	1.23 ± 0.17
Bastug A et al., Turkey [21]	R	ICU transfer	7	145	43	81/64	1.15 ± 0.39	46	71	26/20	1.17 ± 0.41
Bocci MG et al., Italy [22]	P	Survival	5	23	57	17/6	1.07 ± 0.11	17	77	12/5	1.12 ± 0.13
Bonetti G et al., Italy [23]	R	Survival	7	74	62	51/23	1.05 ± 0.07	70	78	45/25	1.14 ± 0.19
Carlino MV et al., Italy [24]	NR	ICU transfer	5	18	47	8/10	1.07 ± 0.05	10	73	8/2	1.12 ± 0.25
Cheng B et al., China [25]	R	Disease progression	7	205	49	71/134	0.98 ± 0.09	251	60	140/111	1.00 ± 0.09
Cheng L et al., China [26]	R	Survival	6	53	54	29/24	1.08 ± 0.15	36	69	20/16	1.12 ± 0.21
Dong Y et al., China [27]	R	Disease severity	7	94	40	34/60	1.01 ± 0.07	53	60	29/24	1.03 ± 0.08
Gong J et al., China [28]	R	Disease severity	5	161	45	89/72	1.03 ± 0.07	28	64	12/16	1.07 ± 0.07
Gue YX et al., UK [29]	R	Disease severity	5	171	67	84/87	1.03 ± 0.07	145	81	104/41	1.10 ± 0.15
Hou W et al., China [30]	R	Disease progression	7	84	47	34/50	1.13 ± 0.07	17	72	10/7	1.10 ± 0.15
Jin X et al., China [31]	R	Disease severity	7	105	NR	NR	0.96 ± 0.10	42	NR	NR	1.21 ± 0.24
Kayina CA et al., India [32]	P	Disease severity	6	215	50	146/69	1.17 ± 0.17	20	51	14/6	1.44 ± 0.32
Ke C et al., China [33]	R	Survival	7	148	60	83/65	1.72 ± 0.72	46	70	32/14	1.39 ± 0.70
Kong M et al., China [34]	R	Disease severity	7	123	53	59/64	1.00 ± 0.15	87	68	45/42	1.00 ± 0.15
Lei P et al., China [35]	R	Disease severity	5	50	65	22/28	1.04 ± 0.07	65	69	36/29	1.07 ± 0.11
Linli Z et al., China [36]	R	Survival	7	142	56	90/52	1.08 ± 0.12	50	68	34/16	1.19 ± 0.13
Liu J et al., China [37]	R	Disease severity	5	27	43	8/19	1.00 ± 0.10	13	60	7/6	1.00 ± 0.10
Lorente L et al., Spain [38]	R	Disease severity	7	118	64	53/65	1.19 ± 0.18	25	71	7/18	1.27 ± 0.19
Luo HC et al., China [39]	R	Survival	6	73	62	39/34	1.03 ± 0.07	12	67	9/3	1.15 ± 0.08
Mertoglu C et al., Turkey [40]	R	ICU transfer	7	532	48	306/226	1.13 ± 0.10	23	59	13/10	1.19 ± 0.19
Mori S et al., Japan [41]	R	Disease severity	5	23	69	13/10	1.08 ± 0.11	22	58	21/1	1.22 ± 0.20
Ponziani FR et al., Italy [42]	R	ICU transfer	7	438	63	263/175	1.04 ± 0.07	77	70	60/17	1.06 ± 0.04
Pourabdollah Toutkaboni et al., Iran [43]	R	Survival	5	456	55	282/174	1.19 ± 0.18	89	64	68/21	1.24 ± 0.15
Sadeghi A et al., China [44]	R	ICU transfer	7	159	57	66/93	1.28 ± 0.51	55	62	30/25	1.60 ± 0.95
Sayad B et al., Iran [45]	NR	Survival	5	35	64	21/14	1.40 ± 0.47	39	67	23/16	1.50 ± 0.72
Shahriarirad R et al., Iran [46]	R	Disease severity	6	102	NR	64/38	1.28 ± 0.15	11	NR	7/4	1.85 ± 0.49
Sun JT et al., China [47]	P	Disease severity	7	49	50	26/23	0.97 ± 0.06	50	71	34/16	1.07 ± 0.15
Tsibouris P et al., Greece [48]	R	Survival	7	45	NR	NR	1.15 ± 0.10	16	NR	NR	1.31 ± 0.29
Wang C et al., China [49]	R	Disease severity	6	35	38	17/18	1.16 ± 0.15	10	43	6/4	1.24 ± 0.32
Wang JH et al., China [50]	R	Survival	7	1074	61	502/572	1.04 ± 0.08	61	74	43/18	1.22 ± 0.15
Xue G et al., China [51]	NR	Disease severity	7	56	61	30/26	0.98 ± 0.07	58	64	34/24	1.01 ± 0.12
Zhang Yaf et al., China [52]	R	Disease severity	7	84	44	29/55	1.15 ± 0.09	31	65	20/11	1.21 ± 0.13
	R		6	54	65	28/26	1.01 ± 0.07	17	68	10/7	1.09 ± 0.07

(*continued on next page*)

Table 1 (*continued*)

				Mild disease or survivor				Severe disease or non-survivor			
Zhang Yan et al., China [53]		Disease progression									
Zhou C et al., China [54]	R	Disease severity	7	95	35	38/57	0.98 ± 0.07	28	40	17/11	0.99 ± 0.07
Zou Y et al., China [55]	R	Disease severity	5	277	50	138/139	1.01 ± 0.06	26	65	20/6	1.06 ± 0.10

Abbreviations: ICU, intensive care unit; NOS, Newcastle-Ottawa quality assessment scale for case-control studies; NR, not reported; P, prospective; R, retrospective.

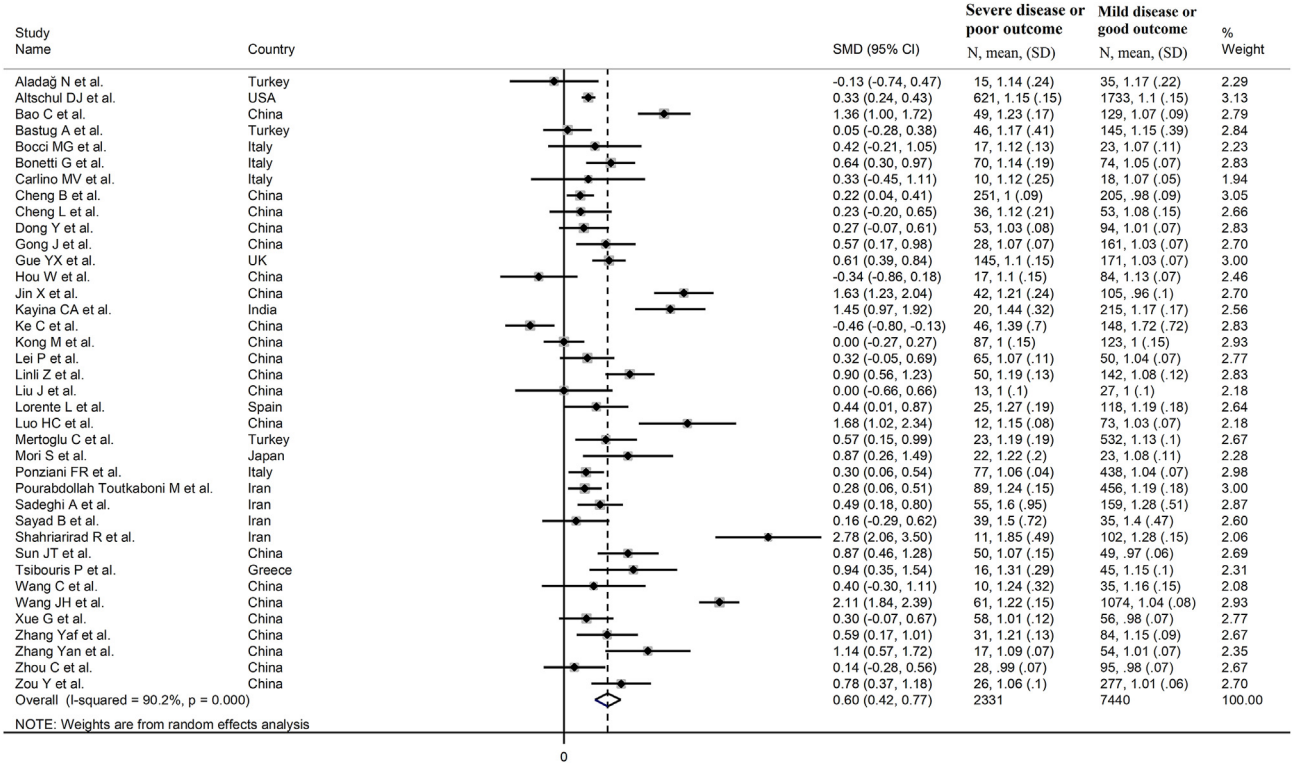

Fig. 2. Forest plot of studies reporting INR values in patients with COVID-19.

Thirty studies were conducted in Asia [18,20,21,25–28,30–37,39–41,43–47,49–55], seven in Europe [22–24,29,38,42,48], and one in America [19]. Thirty-one studies had a retrospective design [18,19,21,23,25–31,33–44,46,48–50,52–55], four were prospective [20,22,32,47], whilst the remaining three did not describe the study design [24,45,51]. Sixteen studies investigated disease severity based on current clinical guidelines [20,27,28,31,34,35,37,38,41,46,47,49,51,52,54,55], three on disease progression [25,30,52], and five on ICU transfer [21,24,40,42,44], whereas the remaining 14 studies investigated survival [18,19,22,23,26,29,32,33,36,39,43,45,48,50]. In all studies, the reported INR was measured within the first 24–48 h from admission.

3.2. Meta-analysis

The overall SMD of the INR between COVID-19 patients with low vs. high severity or survivor vs. non-survivor status is described in Fig. 2. In three studies, patients with high severity or non-survivor status had a lower INR when compared to those with low severity or survivor status (mean difference range, -0.13 to -0.46) [18,30,33]. However, only one study reported a statistically significant difference [33]. There were no differences in two studies (mean difference 0.00) [34,37]. In the remaining studies, the INR was lower in patients with low severity or survivor status (mean difference range, 0.05 to 2.78), with a statistically significant difference reported in 23 studies [19,20,23,25,28,29,31,32,36,38–44,46–48,50,52,53,55].

The pooled results confirmed that the INR values were statistically significantly prolonged in patients with severe disease or non-survivor status (SMD = 0.60, 95 % CI 0.42 to 0.77, $p < 0.001$) (Fig. 2). Extreme heterogeneity between studies was observed ($I^2 = 90.2$ %, $p < 0.001$). The INR values remained statistically significantly prolonged in patients with severe disease or non-survivor status (SMD = 0.55, 95 % CI 0.39 to 0.72, $p < 0.001$; $I^2 = 84.8$ %, $p < 0.001$) after excluding two relatively large studies that accounted for nearly 36 % of the overall sample size [19,50].

Sensitivity analysis, performed by sequentially removing individual studies and re-assessing the pooled estimates, showed that the magnitude and the direction of the effect size were not substantially modified (effect size range, between 0.54 and 0.63) (Fig. 3).

No publication bias was detected with the Begg's ($p = 0.15$) or the Egger's ($p = 0.12$) t-tests. However, the trim-and-fill method identified seven potential missing studies to add to the left side of the funnel plot to ensure symmetry (Fig. 4). The adjusted SMD, albeit attenuated, remained significant (SMD = 0.35, 95 % CI 0.14 to 0.56, $p = 0.001$).

3.3. Meta-regression

Both CRP ($t = 2.07$, $p = 0.048$) and D-dimer ($t = 3.72$, $p = 0.001$) were statistically significantly and positively associated with the pooled SMD. A non-significant trend was also observed with troponin ($t = 2.17$, $p = 0.06$) (Table 2). By contrast, no statistically significant correlations

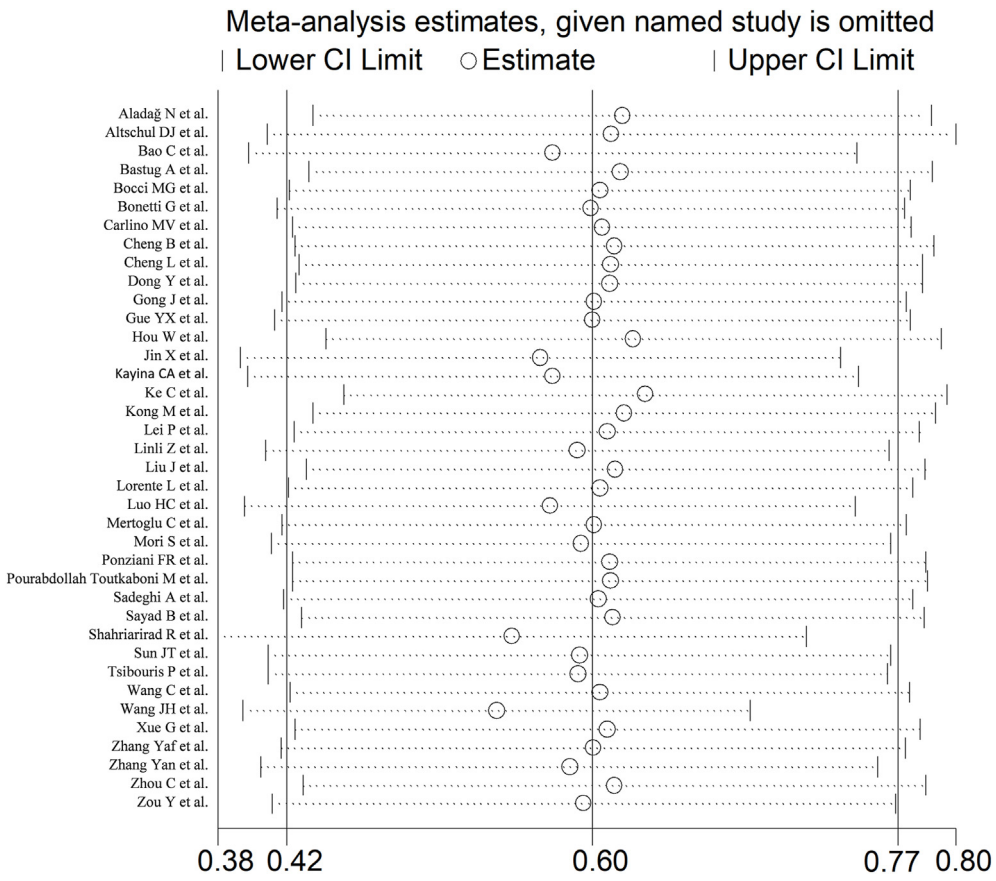

Fig. 3. Sensitivity analysis of the association between INR and COVID-19. The influence of individual studies on the overall standardized mean difference (SMD) is shown. The middle vertical axis indicates the overall SMD, and the two vertical axes indicate the 95 % confidence intervals (CIs). The hollow circles represent the pooled SMD when the remaining study is omitted from the meta-analysis. The two ends of each broken line represent the 95 % CIs.

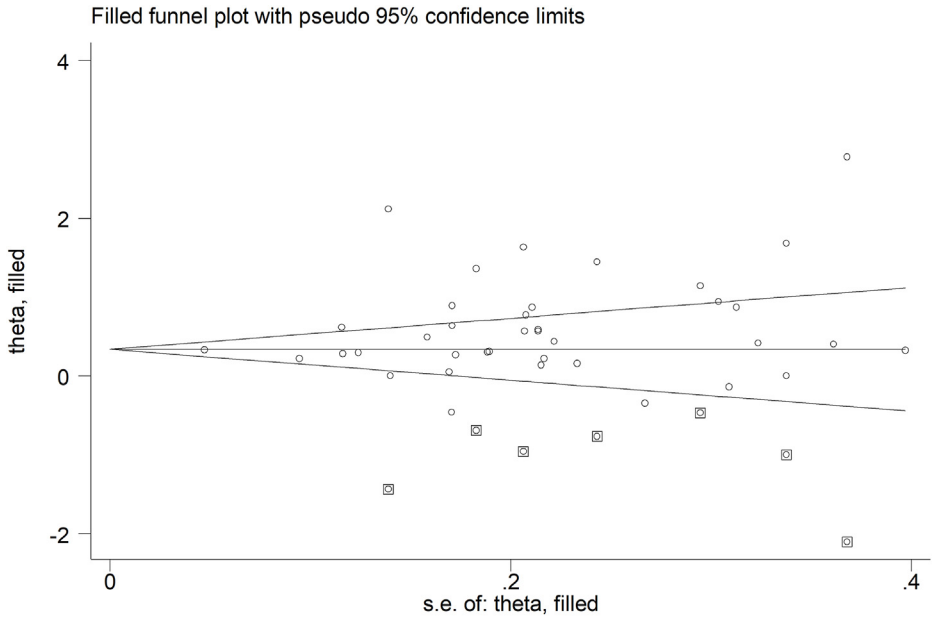

Fig. 4. Funnel plot of studies investigating low vs. high severity or survivor vs. non-survivor status after trimming and filling. Dummy studies and genuine studies are represented by enclosed circles and free circles, respectively.

were observed between the SMD and age (t = -1.3, p = 0.18), gender (t = 0.26, p = 0.80), WBC (t = -0.06, p = 0.96), neutrophils (t = 1.01, p = 0.32), lymphocytes (t = 1.61, p = 0.12), procalcitonin (t = 1.81, p = 0.10), AST (t = -0.27, p = 0.79), ALT (t = -1.19, p = 0.24), albumin (t = 0.08, p = 0.94), LDH (t = 1.20, p = 0.24), CK (t = 1.44, p = 0.18), creatinine (t = 0.13, p = 0.90), urea (t = 0.16, p = 0.88), glucose (t =

Table 2
Univariate meta-regression analysis between effect size and possible contributors to heterogeneity.

Parameter	N	T	p
Age	34	-1.38	0.18
Gender	35	0.06	0.95
White blood cell count	31	-0.06	0.95
Neutrophils	26	1.01	0.32
Lymphocytes	33	1.61	0.12
C-reactive protein	28	2.07	0.048
Procalcitonin	13	1.81	0.10
Aspartate aminotransferase	27	-0.27	0.79
Alanine aminotransferase	29	-1.19	0.24
Albumin	23	0.08	0.94
D-Dimer	26	3.72	0.001
Troponin	11	2.17	0.06
Creatine kinase	13	1.44	0.18
Creatinine	25	0.13	0.90
Urea	22	0.16	0.88
Lactate dehydrogenase	22	1.20	0.24
Glucose	11	1.02	0.33
Activated partial thromboplastin time	24	-0.11	0.91
Fibrinogen	21	-0.69	0.50
Diabetes	22	-0.33	0.74
Cardiovascular disease	19	0.08	0.94
Hypertension	18	-0.32	0.75

1.02, p = 0.33), aPTT (t = -0.11, p = 0.91), fibrinogen (t = -0.69, p = 0.50), diabetes (t = -0.33, p = 0.74), hypertension (t = -0.01, p = 0.99) and cardiovascular disease (t = 0.08, p = 0.94) (Table 2).

In sub-group analysis, the pooled SMD value in retrospective studies (SMD = 0.57, 95 % CI 0.38 to 0.76, p < 0.001; I^2 = 91.0, p < 0.001) was not statistically significantly lower than that observed in prospective studies (SMD = 1.07, 95 % CI 0.66 to 1.48, p < 0.001; I^2 = 68.8, p = 0.02; t = 1.33, p = 0.19). The pooled SMD value in studies evaluating disease severity based on clinical guidelines (SMD = 0.69, 95 % CI 0.39 to 0.98, p < 0.001; I^2 = 87.1, p < 0.001) or survival (SMD = 0.65, 95 % CI 0.31 to 0.98, p < 0.001; I^2 = 94.3, p < 0.001) was not statistically significantly higher than that observed in studies assessing disease progression (SMD = 0.32, 95 % CI -0.33 to 0.97, p = 0.33; I^2 = 85.9, p = 0.001) or ICU admission (SMD = 0.33, 95 % CI 0.16 to 0.51; p < 0.001, I^2 = 21.5, p = 0.28; t = -0.24, p = 0.81) (Fig. 5). Similarly, the pooled SMD value in European studies (SMD = 0.51, 95 % CI 0.37 to 0.65, p < 0.001; I^2 = 9.2 %, p = 0.36) was not statistically significantly lower than that observed in Asian studies (SMD = 0.63, 95 % CI 0.39 to 0.87, p < 0.001; I^2 = 91.9 %, p < 0.001; t = -0.56, p = 0.58) (Fig. 6). A relatively lower heterogeneity was observed in European studies (I^2 = 9.2 %) and in those investigating ICU admission (I^2 = 21.5 %).

4. Discussion

In our systematic review and meta-analysis, COVID-19 patients with severe forms of the disease or those who did not survive during follow-up had significantly prolonged INR values within 24–48 h from admission when compared to patients with milder disease or favorable outcomes. The magnitude of the observed SMD value, 0.60, indicates the presence of a biologically and clinically relevant difference between the groups [56]. Although the between-group heterogeneity was extreme the sequential omission of individual studies did not substantially influence the overall SMD value. Furthermore, there was no evidence of publication bias. The results of the meta-regression analysis suggest that the magnitude of the

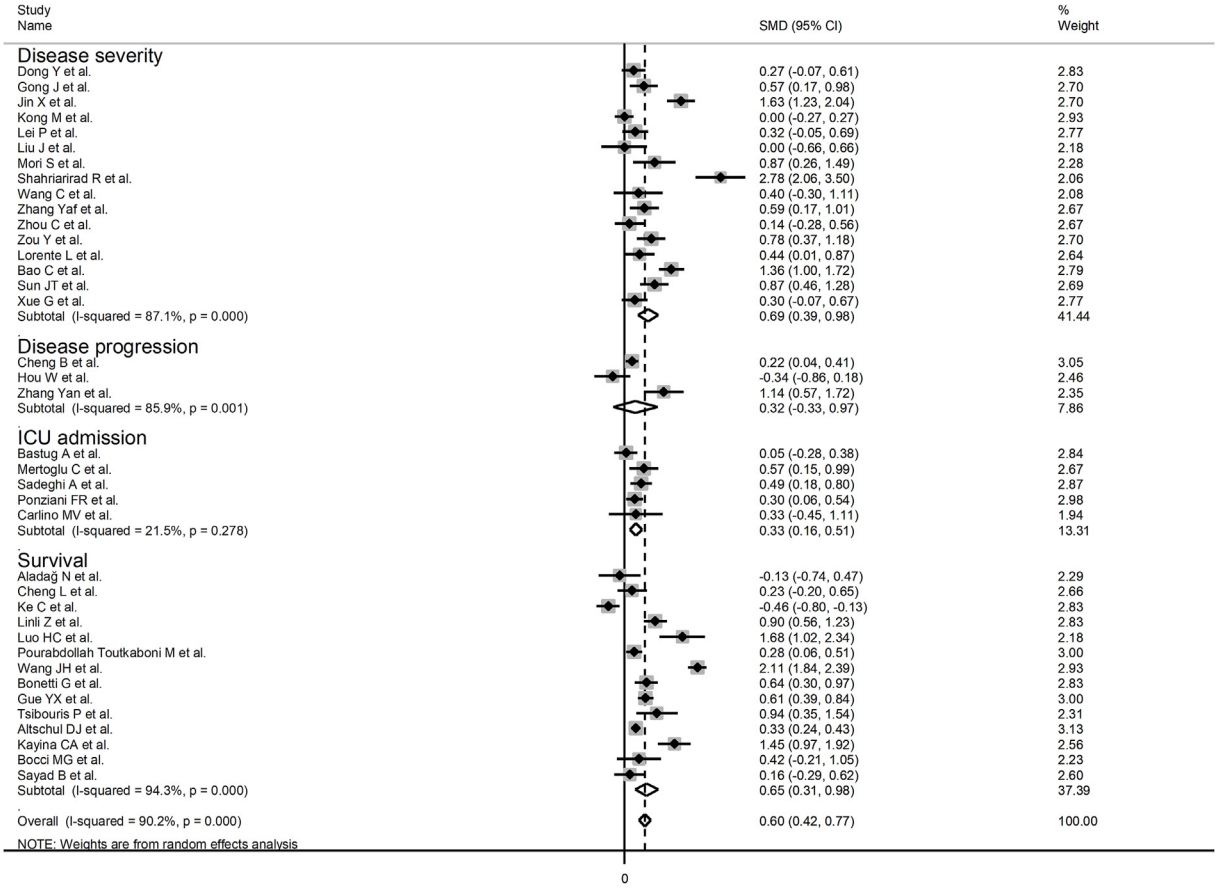

Fig. 5. Forest plot of studies reporting INR values in patients with COVID-19 according to disease severity or survival status. The diamond represents the point estimate and confidence intervals after combining and averaging the individual studies. The vertical line through the vertical points of the diamond represents the point estimate of the averaged studies.

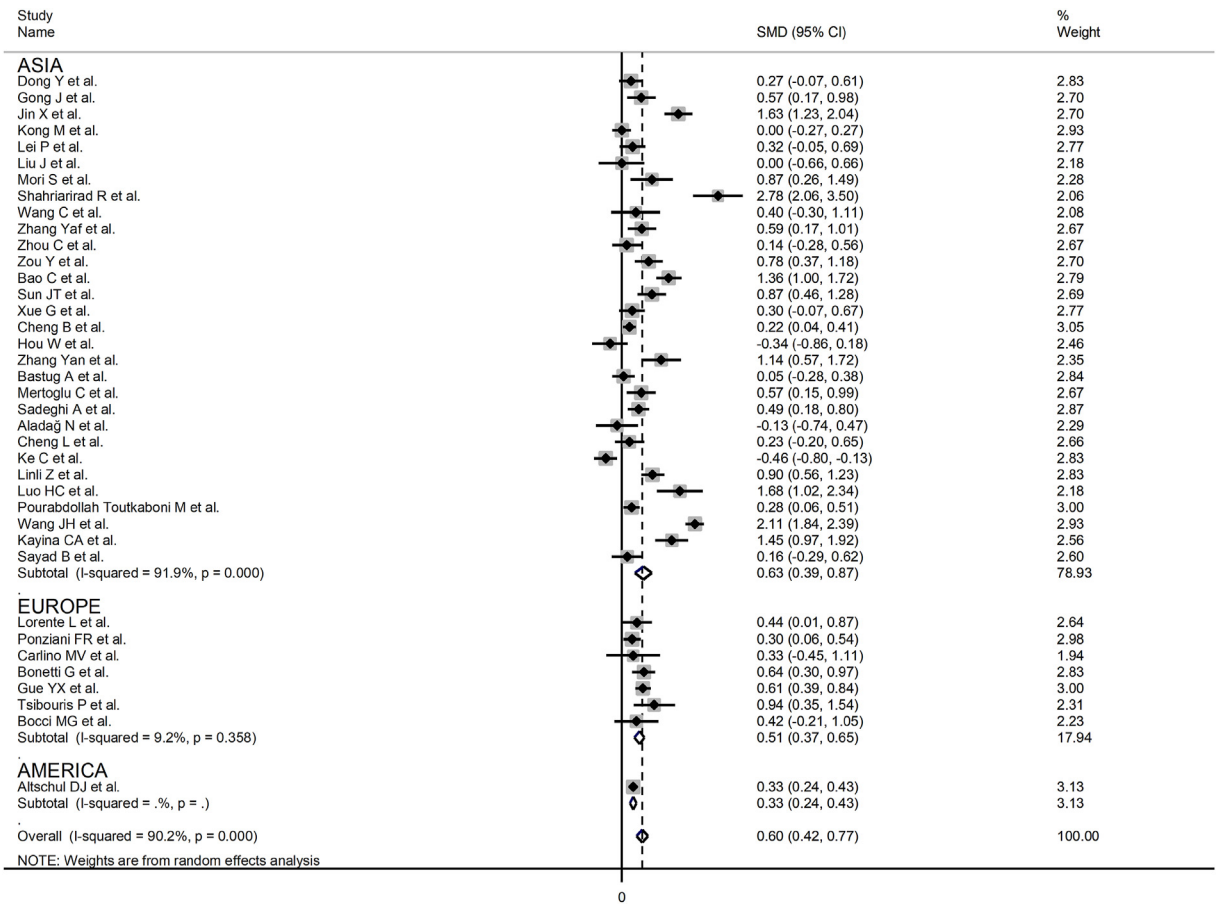

Fig. 6. Forest plot of studies reporting INR values in patients with COVID-19 according to the geographic area where the study was conducted. The diamond represents the point estimate and confidence intervals after combining and averaging the individual studies. The vertical line through the vertical points of the diamond represents the point estimate of the averaged studies.

reported alterations in the INR in severe COVID-19 patients are significantly associated with the D-dimer, an established marker of coagulopathy and poor prognosis in this patient group, and the CRP, reflecting a close interplay between COVID-19-associated coagulopathy and systemic pro-inflammatory state [1,2]. Whilst the lack of significant associations with markers of liver injury (AST and ALT) or synthetic capacity (albumin) suggests that the observed alterations of the INR primarily reflect a state of coagulopathy, additional studies are required to investigate the relationship between the INR and liver dysfunction in COVID-19.

COVID-19-associated coagulopathy is characterized by some unique features that are at least in part driven by the direct interaction between the causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and endothelial cells [3]. As a result, the endothelial von Willebrand factor (VWF) and angiopoietin 2 are released into the circulation with consequent platelet activation and aggregation and stimulation of pro-inflammatory pathways [57,58]. While this phenomenon, and the related thrombus formation, is initially localized in the lungs, the further systemic activation of the coagulation system with thrombosis in multiple organs characterizes the clinical progress of patients with severe COVID-19 [2]. This initial phase of hypercoagulable state, which can be identified using viscoelastic tests [59], is followed by one of consumptive coagulopathy. The latter, paralleled by a shift from pulmonary compromise to multi-organ dysfunction, is characterized by a prolonged PT or INR, in addition to thrombocytopenia and D-dimer elevations [2]. However, while the PT and, consequently, the INR have been thought to be relatively maintained in the early stages of COVID-19, the results of our meta-analysis indicate the presence of significant elevations in these parameters within the first 24–48 of hospitalization, suggesting the presence of consumptive coagulopathy. This observation is supported by recent recommendations for the diagnosis of COVID-19-associated coagulopathy that include the presence of a prolonged PT (>1s) or a prolonged INR (>1.2), in addition to thrombocytopenia (platelet count $<150 \times 10^9$/L), D-dimer elevations (>2 times the upper limit of normal), and presence of clinically overt thrombotic manifestations [2]. However, the mean INR value in patients with severe disease or non-survivor status was >1.2 in only 14 of the 38 identified studies in our meta-analysis [20,31–33,38,41,43–46,48–50,52], suggesting that further studies are required to determine the most accurate cut-off value for diagnostic and prognostic purposes.

4.1. *Limitations of the study*

The extreme between-study heterogeneity in our analyses represents a significant limitation that curtails the generalizability of the results. It is possible that other, unreported, factors might have contributed to the observed heterogeneity. On the contrary, we did not observe publication bias, and the overall effect size was not influenced in sensitivity analysis. Another limitation is related to the fact that none of the selected studies reported serial INR measurements during hospitalization, or their association with severity or clinical outcomes. This warrants further research as a study conducted in the early phases of the COVID-19 pandemic has shown the presence of significant differences in the temporal patterns of both PT and D-dimer, based on measurements performed on day 1, 4, 7, 10, and 14 after admission, between survivors and non-survivors. In particular, non-survivors had significantly longer PT values and higher D-dimer concentrations at day 1, 10 and 14 [60].

5. Conclusions

Our systematic review and meta-analysis with meta-regression has shown that prolonged INR values, indicating the presence of systemic coagulopathy, are significantly associated with severe disease and increased mortality in patients with COVID-19. Additional studies are required to determine whether single or serial INR measurements, with or without D-dimer and other clinical and demographic characteristics, can further enhance early risk stratification and management strategies, and indicate the presence of liver dysfunction in this group.

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The author contribution

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Data Interpretation: Angelo Zinellu, Panagiotis Paliogiannis, Ciriaco Carru, Arduino A Mangoni.

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Declaration of competing interest

The authors declare no conflict of interests.

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