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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Original research article

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

Angelo Zinella, Panagiotis Paliogiannis, Ciriaco Carru, Arduino A. Mangoni

Department of Biomedical Sciences, University of Sassari, Sassari, Italy
Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy
Discipline of Clinical Pharmacology, College of Medicine and Public Health, Flinders University, Adelaide, Australia
Department of Clinical Pharmacology, Flinders Medical Centre, Southern Adelaide Local Health Network, Adelaide, Australia

ARTICLE INFO

Keywords:
International normalized ratio
Coagulopathy
COVID-19 severity
Mortality

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 (I² = 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
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, ≥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 ≥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 I² statistic: I² < 25 %, no heterogeneity; I² between 25 % and 50 %, moderate heterogeneity; I² between 50 % and 75 %, large heterogeneity; and I² > 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 (creatinine 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.

![Flow chart of study selection](image_url)
Table 1
Characteristics of the studies included in the meta-analysis.

| 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) |
|-----------------------------|--------------|----------|-------------|---|-------------|---------------|----------------|---|-------------|---------------|----------------|
| Aladag 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          | 26/60         | 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 |
| Carlini MV et al., Italy [24] | R            | Disease progression | 7 | 205 | 49        | 71/134        | 0.98 ± 0.09 | 251 | 60          | 140/111       | 1.00 ± 0.09 |
| Cheng B et al., China [25]  | R            | Survival | 6 | 53 | 54        | 29/24         | 1.08 ± 0.15 | 36 | 69          | 20/16         | 1.12 ± 0.21 |
| Cheng L et al., China [26]  | R            | Disease severity | 7 | 94 | 40        | 34/60         | 1.01 ± 0.07 | 53 | 60          | 29/24         | 1.03 ± 0.08 |
| Dong Y et al., China [27]   | R            | Disease severity | 7 | 161 | 45        | 89/72         | 1.03 ± 0.07 | 28 | 64          | 12/16         | 1.07 ± 0.07 |
| Gong J et al., China [28]   | R            | Disease severity | 5 | 171 | 67        | 84/87         | 1.03 ± 0.07 | 145 | 81          | 104/41        | 1.10 ± 0.15 |
| Gu YX et al., UK [29]       | R            | Disease severity | 5 | 84 | 47        | 34/50         | 1.13 ± 0.07 | 17 | 72          | 10/7          | 1.10 ± 0.15 |
| Hou W et al., China [30]    | R            | Disease progression | 7 | 105 | NR        | NR           | 0.96 ± 0.10 | 42 | NR          | NR           | 1.21 ± 0.24 |
| Jin X et al., China [31]    | R            | Disease severity | 6 | 215 | 50        | 146/69        | 1.17 ± 0.17 | 20 | 51          | 14/6         | 1.44 ± 0.32 |
| Kayina CA et al., India [32] | R            | Survival | 7 | 148 | 60        | 83/65         | 1.72 ± 0.72 | 46 | 70          | 32/14         | 1.39 ± 0.70 |
| Ke C et al., China [33]     | R            | Disease severity | 7 | 123 | 53        | 59/64         | 1.00 ± 0.15 | 87 | 68          | 45/42         | 1.00 ± 0.15 |
| Kong M et al., China [34]   | R            | Disease severity | 5 | 50 | 65        | 22/28         | 1.04 ± 0.07 | 65 | 69          | 36/29         | 1.07 ± 0.11 |
| Lei P et al., China [35]    | R            | Disease severity | 5 | 142 | 56        | 90/52         | 1.08 ± 0.12 | 50 | 68          | 34/16         | 1.19 ± 0.13 |
| Linli Z et al., China [36]  | R            | Disease severity | 5 | 27 | 43        | 8/19          | 1.00 ± 0.10 | 13 | 60          | 7/6          | 1.00 ± 1.00 |
| Liu J et al., China [37]    | R            | Disease severity | 7 | 118 | 64        | 53/65         | 1.19 ± 0.18 | 25 | 71          | 7/18         | 1.27 ± 0.19 |
| Lorente L et al., Spain [38] | R            | Survival | 6 | 73 | 62        | 39/34         | 1.03 ± 0.07 | 12 | 67          | 9/3          | 1.15 ± 0.08 |
| Luo HC et al., China [39]   | R            | Disease severity | 7 | 532 | 48        | 306/226       | 1.13 ± 0.10 | 23 | 59          | 13/10         | 1.19 ± 0.19 |
| Mertoglu C et al., Turkey [40] | R            | ICU transfer | 7 | 23 | 69        | 13/10         | 1.08 ± 0.11 | 22 | 58          | 21/1         | 1.22 ± 0.20 |
| Mori S et al., Japan [41]   | R            | Disease severity | 7 | 438 | 63        | 263/175       | 1.04 ± 0.07 | 77 | 70          | 60/17         | 1.06 ± 0.04 |
| Ponziani FR et al., Italy [42] | R            | ICU transfer | 5 | 456 | 55        | 282/174       | 1.19 ± 0.18 | 89 | 64          | 68/21         | 1.24 ± 0.15 |
| Pourabdollah T, Tootkaboni et al., Iran [43] | R | ICU transfer | 7 | 159 | 57        | 66/93         | 1.28 ± 0.51 | 55 | 62          | 30/25         | 1.60 ± 0.95 |
| Sadeghi A et al., China [44] | R            | Survival | 5 | 35 | 64        | 21/14         | 1.40 ± 0.47 | 39 | 67          | 23/16         | 1.50 ± 0.72 |
| Sayad B et al., Iran [45]   | NR           | Survival | 5 | 102 | NR        | 64/38         | 1.28 ± 0.15 | 11 | NR          | 7/4          | 1.85 ± 0.49 |
| Shahriarizad R et al., Iran [46] | R | Disease severity | 5 | 49 | 50        | 26/23         | 0.97 ± 0.06 | 50 | 71          | 34/16         | 1.07 ± 0.15 |
| Sun JT et al., China [47]   | R            | Survival | 6 | 35 | 38        | 17/18         | 1.16 ± 0.15 | 10 | 43          | 6/4          | 1.24 ± 0.32 |
| Toubouri P et al., Greece [48] | R | Survival | 7 | 56 | 61        | 30/26         | 0.98 ± 0.07 | 58 | 64          | 34/24         | 1.01 ± 0.12 |
| Wang C et al., China [49]   | R            | Disease severity | 7 | 1074 | 61 | 502/572 | 1.04 ± 0.08 | 61 | 74          | 43/18         | 1.22 ± 0.15 |
| Wang JH et al., China [50]  | R            | Survival | 6 | 56 | 61        | 30/26         | 0.98 ± 0.07 | 58 | 64          | 34/24         | 1.01 ± 0.12 |
| Xue G et al., China [51]    | NR           | Disease severity | 7 | 84 | 44        | 29/55         | 1.15 ± 0.09 | 31 | 65          | 20/11         | 1.21 ± 0.13 |
| Zhang Yaf et al., China [52] | R            | Disease severity | 6 | 54 | 65        | 28/26         | 1.01 ± 0.07 | 17 | 68          | 10/7         | 1.09 ± 0.07 |

(continued on next page)
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

| Study Name | Country | Disease severity | N, mean (SD) | N, mean (SD) | Weight |
|------------|---------|------------------|--------------|--------------|--------|
| Ali et al. | Turkey  | NA               |              |              |        |
|-management studies for case-control studies; NR, not reported; P, prospective; R, retrospective. 

Table 1 (continued)

### Abbreviations

ICU, intensive care unit; NOS, Newcastle-Ottawa quality assessment scale; NR, not reported; P, prospective; R, retrospective.
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 ($t = 0.38$).
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; I² = 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; I² = 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; I² = 87.1, p < 0.001) or survival (SMD = 0.65, 95 % CI 0.31 to 0.98, p < 0.001; I² = 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; I² = 85.9, p = 0.001) or ICU admission (SMD = 0.33, 95 % CI 0.16 to 0.51; p < 0.001; I² = 21.5, p = 0.28; t = -0.24, p = 0.81) (Fig. 5). Similarly, the pooled SMD value in European studies (SMD = 0.63, 95 % CI 0.39 to 0.87, p < 0.001; I² = 91.9, p < 0.001; t = -0.56, p = 0.58) (Fig. 6). A relatively lower heterogeneity was observed in European studies (I² = 92.5 %) and in those investigating ICU admission (I² = 21.5 %).

### Table 2

| 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 | 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; I² = 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; I² = 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; I² = 87.1, p < 0.001) or survival (SMD = 0.65, 95 % CI 0.31 to 0.98, p < 0.001; I² = 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; I² = 85.9, p = 0.001) or ICU admission (SMD = 0.33, 95 % CI 0.16 to 0.51; p < 0.001; I² = 21.5, p = 0.28; t = -0.24, p = 0.81) (Fig. 5). Similarly, the pooled SMD value in European studies (SMD = 0.63, 95 % CI 0.39 to 0.87, p < 0.001; I² = 91.9, p < 0.001; t = -0.56, p = 0.58) (Fig. 6). A relatively lower heterogeneity was observed in European studies (I² = 92.5 %) and in those investigating ICU admission (I² = 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](https://via.placeholder.com/150) 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.
reported alterations in the INR in severe COVID-19 patients are signifi-
cantly associated with the D-dimer, an established marker of coagulopathy
and poor prognosis in this patient group, and the CRP, re-l ecting a close
interplay between COVID-19-associated coagulopathy and systemic
pro-in
fl ammatory state [1,2]. Whilst the lack of signi-
fi cant associations
with markers of liver injury (AST and ALT) or synthetic capacity (albumin)
suggests that the observed alterations of the INR primarily re-l ect a state of
coagulopathy, additional studies are required to investigate the relation-
ship 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 circu-
lation with consequent platelet activation and aggregation and stimula-
tion of pro-in
fl ammatory 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
identifi ed by using viscoelastic tests [59], is followed by one of consump-
tive coagulopathy. The latter, paralleled by a shift from pulmonary com-
proromise 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 signifi cant elevations in these
parameters within the fi rst 24–48 of hospitalization, suggesting the

4.1. Limitations of the study
The extreme between-study heterogeneity in our analyses represents
a signifi cant 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 infl uenced in sensitivity analysis.
Another limitation is related to the fact that none of the selected studies
reported serial INR measurements during hospitalization, or their asso-
ciation 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 signifi cant 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 signifi cantly 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.

Financial disclosure

This research was supported by a Visiting Professorship awarded to Professor Arduino A Mangoni by the University of Sassari, Italy.

The author contribution

Study Design: Angelo Zinellu, Panagiotsi Paliogiannis, Ciriaco Carru, Arduino A Mangoni.

Data Collection: Angelo Zinellu, Panagiotsi Paliogiannis.

Statistical Analysis: Angelo Zinellu, Panagiotsi Paliogiannis.

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

Manuscript Preparation: Arduino A Mangoni.

Literature Search: Angelo Zinellu, Panagiotsi Paliogiannis.

Funds Collection: n/a.

Declaration of competing interest

The authors declare no conflict of interests.

References

[1] Fajenbaum DC, June CH. Cytokine storm. N Engl J Med 2020;383:2255–73.
[2] Iba T, Warkentin TE, Thachil J, Levy M, Leip M, Levy JH. Proposal of the de
[3] Giordo R, Paliogiannis P, Mangoni AA, Pintus G. SARS-CoV-2 and endothelial cell interaction in COVID-19: molecular perspectives. Vasc Biol 2021;3:815–21.
[4] Asakura H, Ogawa H. COVID-19-associated coagulopathy and disseminated intravascular coagulation. Int J Hematol 2021;113:45–57.
[5] Weitz JI, Fredenburgh JC, Eikelboom JW. A test in context: D-dimer. J Am Coll
[6] Iba T, Warkentin TE, Thachil J, Levy M, Leip M, Levy JH. Proposal of the de
[7] Hirsh J, Poller L. The international normalized ratio. A guide to understanding and
[8] Iba T, Levy JH, Levi M, Thachil J, Levy JH. Coagulopathy in COVID-19. J Thromb Haemostasis 2020;18:2103–20.
[9] Kong M, Zhang H, Cao X, Mao X, Lu Z. Higher level of neutrophil-to-lymphocyte ratio significantly correlated with COVID-19 severity. J Clin Hematol 2020;14:733–40.
[10] Pei L, Zhang L, Han P, Zheng C, Tong Q, Shang H, Yang F, Hu Y, Li X, Song Y. Liver injury in patients with COVID-19: clinical profiles, CT findings, the correlation of the severity with liver injury. Hepatol Int 2020;14:733–42.
[11] Linli Z, Chen Y, Tian G, Guo S, Fei Y. Identifying and quantifying robust risk factors for mortality in critically ill patients with COVID-19 using quantile regression. Am J Emerg Med 2021 Jul;45:345–51. https://doi.org/10.1016/j.ajem.2020.08.090.
[12] Liu J, Li S, Liu J, Liang B, Wang X, Wu H, Li W, Tong Q, Yi J, Liu Z, Xiong L, Guo C, Tian J, Luo J, Yao P, Peng H, Chen J, Li C, Li Q, Guo Z, Li X, Wu J, Li X, Wu J, Lv S, Wang B, Weng Z, Han C, Zhu H, Zhou R, Zhou H, Chen X, Pe Y, Zhu B, Wang L, Zhou W, He S, He Y, Jie S, Wei P, Zhang J, Lu Y, Wang W, Zhang L, Li Z, Zhou F, Wang Y, Dittmer U, Hu Y, Yang D, Zhang X, Zhao H. Clinical characteristics, laboratory findings, the correlation of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. Elife 2020;9:20276. https://doi.org/10.7554/eLife.10276.
[13] Lorenz L, Martin MM, Argueso M, Sole-Vilajosana J, Perez A, Marcaju YM, Ramos-Gomez I, Lopez S, Franco A, González-Rivero AF, Martin M, Gonzalez V, Alcobia-Flores J, Rodriguez-Mario R, Riano-Ruiz M, Guilleremo O, Gonzalez I, Cantera T, Ortiz-Lopez R, Ojeda N, Rodriguez-Perez A, Dominguez-Gomez A, Jiménez A. Association between red blood cell distribution width and mortality of COVID-19 patients. Anaerobe 2020;52:100921.
[14] Luo HC, You CY, Lu SW, Fu YQ. Characteristics of coagulation alteration in patients with COVID-19. Am J Hematol 2021;100:45–52.
[15] Mertoglu C, Huyut MT, Aylan C, Ceylan G, Coban TA. How do routine laboratory tests change in coronavirus disease 2019? Scand J Clin Lab Invest 2021:81:24–33.
[16] Mori S, Ai T, Otomo Y. Characteristics, laboratory, and prognosis of severe COVID-19 in the Tokyo metropolitan area: a retrospective case series. PloS One 2020;15:e239644.
Ponziani FR, Del Zompo F, Nesli A, Santopao F, Iaino G, Pompili M, Gashbarrini A. Genelli against C-g. Liver involvement is not associated with mortality: results from a large cohort of SARS-CoV-2-positive patients. Aliment Pharmacol Ther 2020;52:1060–8.

Pourabdollah Toutkaboni M, Askari E, Khalili N, Tabarsi P, Jamaati H, Velayati AA, Doralulina A, Rezaei M, Nadji SA, Mohammadia A, Khalili N. Demographics, laboratory parameters and outcomes of 1061 patients with coronavirus disease 2019: a report from Tehran, Iran. New Microbes New Infect 2020 Nov;38:100777. https://doi.org/10.1016/j.nmni.2020.100777.

Sadeghi A, Estami P, Dooghie Moghadam A, Piruzehi A, Shojaei S, Vahidi M, Soheili A, Ghanimat F, Keshmiri Y, Abdi S, Zali MR. COVID-19 and ICU admission associated predictive factors in Iranian patients. Caspian J Intern Med 2020;11: 512–9.

Sayad B, Rahimi Z. Blood coagulation parameters in patients with severe COVID-19 from Kermanshah Province, Islamic Republic of Iran. East Mediterr Health J 2020; 26:999–1004.

Shahriarirad R, Khodamoradi Z, Erfani A, Hosseinpour H, Ranjbar K, Emami Y, Mirahmadizadeh A, Lotfi M, Shirazi Yaghoobeh B, Dorrani Nejad A, Hemmati A, Ebrahimzadeh M, Moghadam M. Epidemiological and clinical features of 2019 novel coronavirus diseases (COVID-19) in the South of Iran. BMC Infect Dis 2020; 20:427.

Sun JT, Chen Z, Nie P, Ge H, Shen L, Yang P, Qu XL, Ying XY, Zhou Y, Wang W, Zhang M, Fu J. Lipid Profile features and their associations with disease severity and mortality in patients with COVID-19. Front Cardiovasc Med 2020;7:584987.

Xue G, Gan X, Wu Z, Xie D, Xiong Y, Hua L, Zhou B, Zhou N, Xiang J, Li J. Novel serological biomarkers for inflammation in predicting disease severity in patients with COVID-19. Int Immunopharmacol. 2020;89:107065.

Zhang Y, He L, Chen H, Lu S, Xiong Y, Liu J, Zheng Y, Wang S, Liu L. Manifestations of blood coagulation and its relation to clinical outcomes in severe COVID-19 patients: retrospective analysis. Int J Lab Hematol. 2020;42:766–72.

Zhou C, Huang Z, Tan W, Li X, Yin W, Xiao Y, Tao Z, Geng S, Hu Y. Predictive factors of severe coronavirus disease 2019 in previously healthy young adults: a single-center, retrospective study. Respir Res. 2020;21:157.

Zou Y, Guo H, Zhang Y, Zhang Z, Liu Y, Wang J, Lu H, Qian Z. Analysis of coagulation parameters in patients with COVID-19 in Shanghai, China. Biosci Trends. 2020;14:285–9.

Cohen J. Statistical Power Analysis for the Behavioral Sciences. second ed. Hillsdale, NJ, USA: Erlbaum; 1988.

Ward SE, Carley GF, Lavins M, Fogarty H, Karampini E, McEvoy NL, Clarke J, Boylan M, Alalqam R, Kelly C, de Barra E, Glavey S, Ni Cheallaigh C, Begrin C, Martin-Loeches I, Townsend L, Mallon PW, O’Sullivan JM, O’Donnell JS, Irvine C. VWF. Von Willebrand factor propeptide in severe coronavirus disease 2019 (COVID-19): evidence of acute and sustained endothelial cell activation. Br J Haematol. 2021;192:714–9.

Pine AB, Meizlish ML, Goshua G, Chang CH, Zhang H, Bishai J, Bahel P, Patel A, Ghyli R, Kwan JM, Won CH, Price C, Dela Cruz CS, Halene S, van Dijk D, Hwa J, Lee AL, Chun HJ. Circulating markers of angiogenesis and endotheliopathy in COVID-19. Palm Circ Res. 2020:10. 2045894020966547.

Spiezia L, Campello E, Cola M, Polletto F, Cerruti L, Poretto A, Simion C, Cattelan A, Vettor R, Simioni P. More severe hypercoagulable state in acute COVID-19 pneumonia as compared with other pneumonia. Mayo Clin Proc. 2020;85:696–702.

Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemostasis. 2020;18:844–7.