



ABSTRACT

We evaluated the effect of D-dimer levels in COVID-19 patients on the disease severity. This study pooled all available relevant studies selected from PubMed-MEDLINE, Web of Science, and EMBASE and calculated standardized mean difference (SMD) of D-dimer levels between paired groups of COVID-19 patients. Out of 632 articles identified during literature search, 43 original studies including 9861 patients from 11 different countries were included in a meta-analysis. This analysis revealed that D-dimer levels significantly increased with increasing severity of COVID-19. Thus, a comparison between 'severe/critical versus general' groups gave a D-dimer level standardized mean difference (SMD) of 1.31 (95% CI: 0.85 to 1.76), $P < 0.000001$; $I^2 = 96\%$, and a SMD of 1.13 (95% CI: 0.91 to 1.36), $P < 0.000001$; $I^2 = 91\%$ between 'non-survivor and survivor' groups of COVID-19 patients. In addition, an increase in D-dimer level from 2 folds to 37 folds (median value: 7 folds) was found to be associated with COVID-19 related pathogenic severity and mortality. These data confirms D-dimer as a reliable biomarker for the patient management and anticoagulation based therapeutics.

INTRODUCTION

- Severe Acute Respiratory Syndrome Corona Virus-2 (SARS CoV-2) is a virus originated from Wuhan, China as a causative agent of COVID-19 claiming millions of lives across the globe. As fatality rate of COVID-19 hugely depend on clinical severity, it is imperative to find a reliable prognostic marker to monitor the disease and to apply suitable therapeutic strategies on this basis.
- D-dimer is a small protein fragment created by degradation of blood clot via fibrinolysis. Various recent studies have indicated that elevated level of D-dimer potentially serves as a predictor of disease severity and/or mortality in COVID-19 patients. Nevertheless, due to considerable variation in reporting units of this assay, no stand-alone universal cut-off exists to use as a guideline for therapeutic purposes. Though some of the meta-analysis based studies already exist on this topic, they either used very low number of studies or almost all China-based studies, thus lacking statistical strength and/or universal representativeness of data.

Goal of the Study:

- To combine all available eligible studies to confirm or refute the prognostic role of D-dimer in COVID-19 related disease severity and mortality
- To analyze a bigger pool of studies to ensure a more global representativeness of the data, and to predict more reliable cut-off based on this information.

METHODS

- This meta-analysis reviewed all relevant articles available until 02/20/2021 using PubMed-MEDLINE, Web of Science, EMBASE and other resources following PRISMA guidelines and using Cochrane's Review Manager software (RevMan 5.3).
- Keywords used for literature search were: "COVID-19", "Severe Acute Respiratory Syndrome Corona Virus 2", "SARS CoV-2", "D-dimer" and "Fibrin fragment D".
- For selected articles, random effect model was used to calculate standardized mean difference (SMD) between the comparison groups using mean and SD data. Mean and SD were either directly taken from the article or calculated from provided median and IQR values as per the guidelines of Wan et al, 2014.
- Comparison groups used for SMD calculation are: non-survivor vs survivor and Severe/Critical vs General groups.
- Study specific elevation in D-dimer level from ULN (upper limit normal) was calculated in terms of the ratio of mean to ULN of the assay where applicable

RESULTS

- Number of Articles selected after full-text review: 43 out of 632
- Sites of Study: 11 different countries representing Europe, Asia and America
- Overall effect with Z values of 5.62 and 10.02 were noticed for 'Severe/Critical vs General' group and 'Non-survivor vs Survivor' group respectively.
- Spike of D-dimer in terms 'mean to ULN' ratio in severe/critical or non-survivor patients was in the range of **2 to 37 folds** (median value: 7 folds) (n=13)

Schematic Representation of Systematic Search of Studies as per PRISMA Guidelines

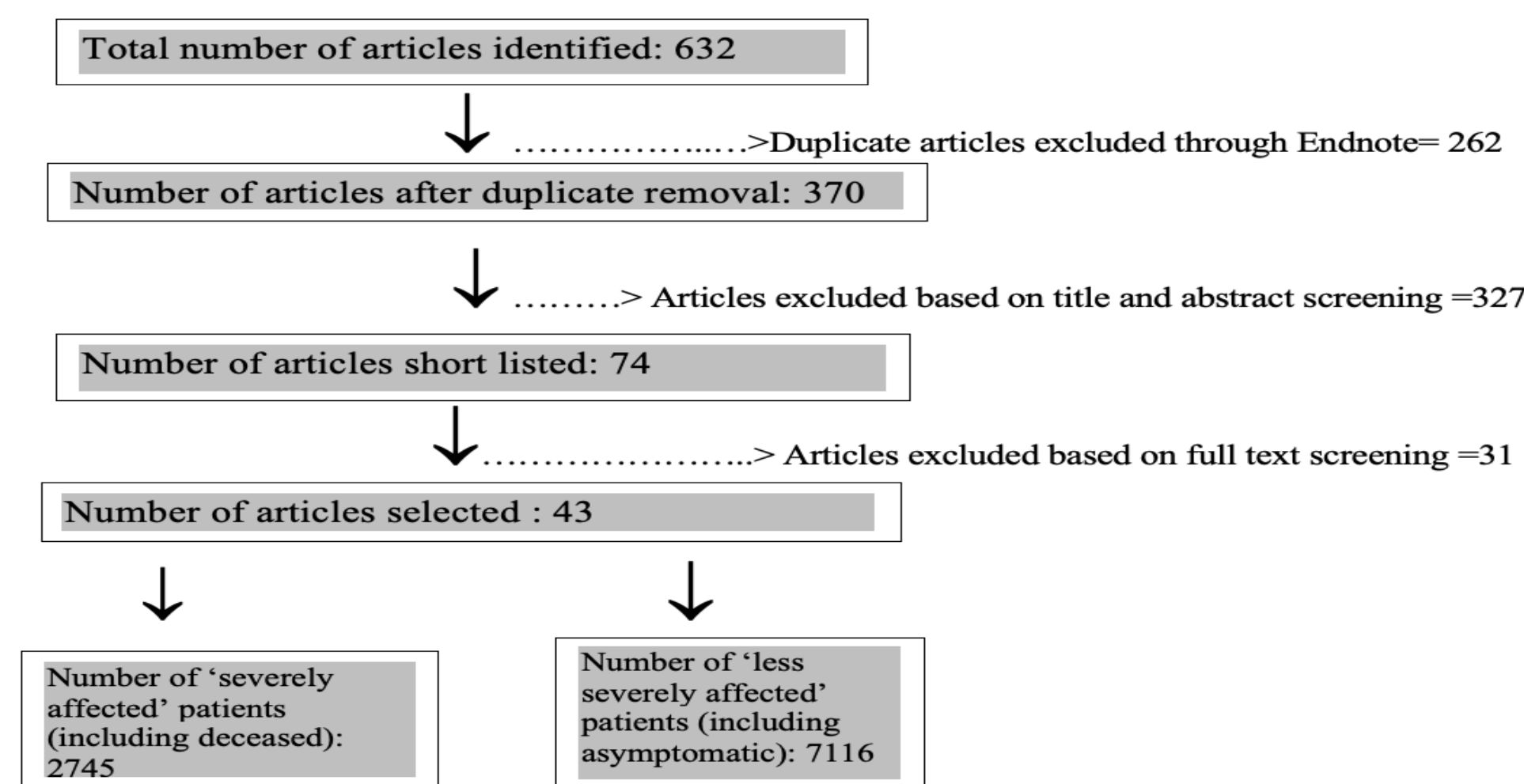


Figure 1: Schematic representation of systematic search of studies as per PRISMA Guidelines

D-dimer Level Severe/Critical vs General Group of COVID-19 Patients (SMD)

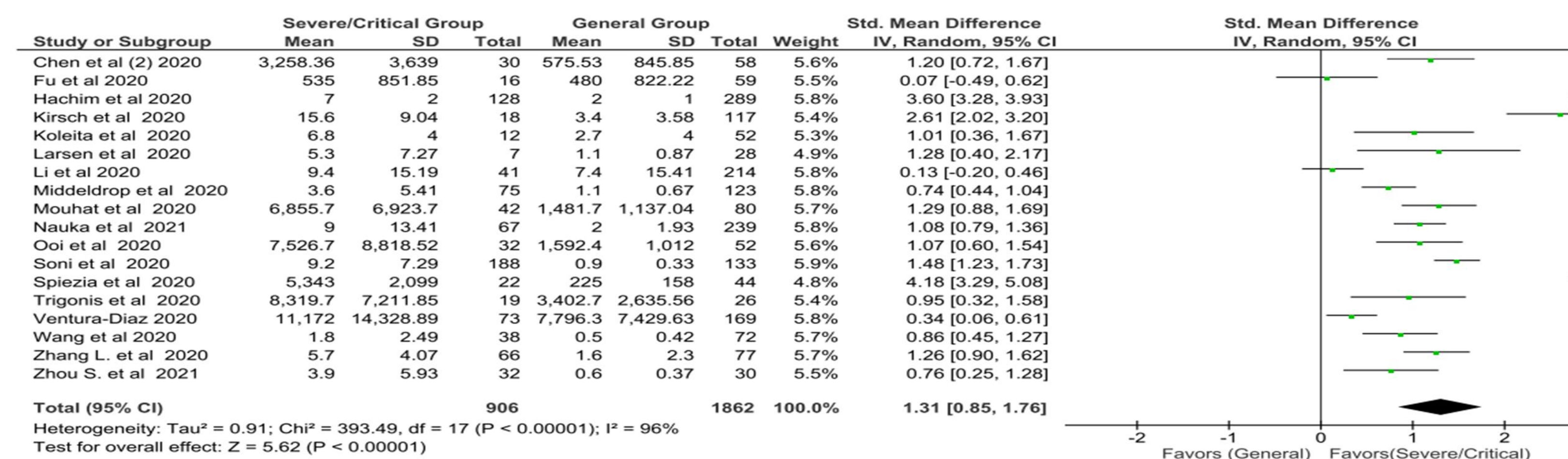


Figure 2: Forest plot showing Standardized mean difference of D-dimer level of Severe/Critical vs General group of COVID-19 patients (Note: SD: Standard deviation, CI: Confidence interval)

D-dimer Level : Non-survivor vs Survivor Patients of COVID-19 (SMD)

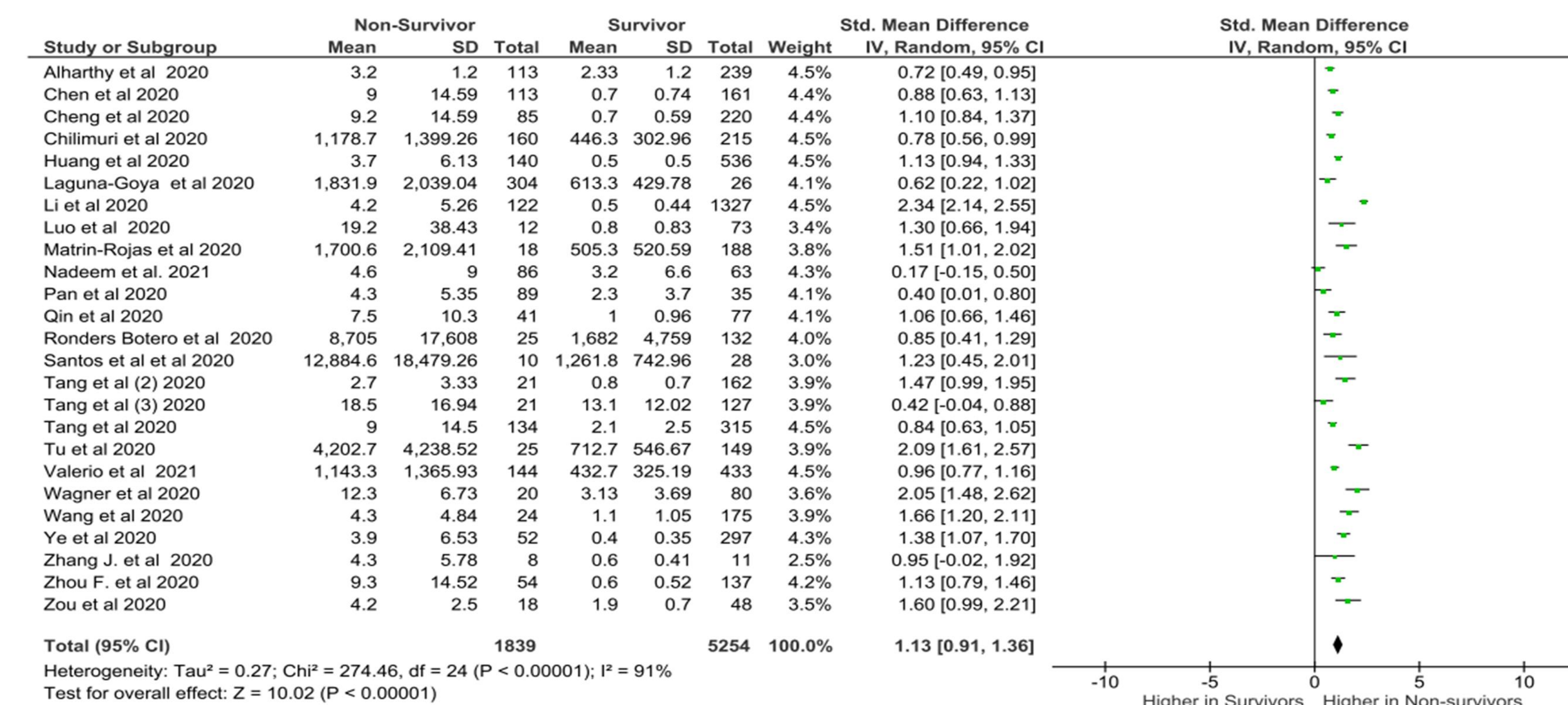


Figure 3: Forest plot showing Standardized mean difference of D-dimer level of Non-survivor and Survivor COVID-19 patients (Note: SD: Standard deviation, CI: Confidence interval)

CONCLUSIONS

- The results of this meta-analysis indicates that :
- D-dimer serves as a predictor of pathogenic severity or mortality in COVID-19 patients.
 - SMD of D-dimer level on both comparison groups shows statistically significant results ($p < 0.00001$).
 - The studies analyzed had a high level of heterogeneity with I-squared values ranging from 91 to 96%.

DISCUSSION AND FUTURE DIRECTION

- Though this meta-analysis confirmed that D-dimer serves as a promising prognostic marker of COVID-19 related severity and mortality, a high level of heterogeneity, as depicted by forest plots, exists among these studies.
- Heterogeneity is attributed to the study design itself and use of diverse units across the studies.
- Since only 4 out of 43 studies specify whether the type of unit was FEU or DDU, interconversion of the unit was not possible to use a consensus unit for this meta analysis. As such, instead of absolute universal cut-off, a relative cut off value in terms of 'folds of ULN' was calculated.
- As indicated by this study, the D-dimer spike of $\geq 2x$ ULN could be used as a supportive guideline to predict the starting point of disease severity/mortality and initiation of anticoagulation therapy.
- Being a broad study capturing data from different parts of globe including 7 studies from USA (New York, Texas, and Indiana), 10 studies from Europe (Spain, France, Netherlands, UK, Italy and Germany) and 26 studies from Asia (China, India, Saudi Arabia, and UAE), this meta-analysis includes very representative data.
- In addition, this study has been able to raise a very significant issue of lack of harmonization of D-dimer assay.
- In the scenario of current use of CT Pulmonary Angiogram and Doppler ultrasound to rule out COVID-19 related pulmonary embolism (PE) and deep vein thrombosis (DVT); D-dimer might replace these tools as a possible less expensive alternative.
- In addition, anti-coagulation therapy could be standardized as a part of COVID-19 treatment with the guidance of D-dimer level.
- The biggest hurdle for the universality of D-dimer assay is lack of harmonization/standardization. Standardization of this assay in terms of International Normalized Ratio (INR), like in the case of Prothrombin Time assay, using a suitable universal standard material could potentially circumvent the limitation of differences on assay platform, calibration range and use of diverse reporting units.

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Correspondence to : Ramesh Paneru,
 Email: Ramesh.paneru@stonybrook.edu, rpaneru7@gmail.com