Evaluation of D-dimer as a Prognostic Marker of COVID-19 Related Severity and Mortality

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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 9611 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: 0.65 to 1.76), P<0.00001; P=96%, and a SMD of 1.13 (95% CI: 0.91 to 1.36), P<0.00001; P=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 as D-dimer as a reliable biomarker for the patient management and anticoagulation based therapeutics.

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’ groups 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)

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

Figure 2: Forest plot showing standardized mean difference of D-dimer level of Severe/Critical vs General Group of COVID-19 Patients (SMD)

Figure 3: Forest plot showing standardized mean difference of D-dimer level of Non-survivor vs Survivor Group of COVID-19 Patients (SMD)

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 ->2xULN 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 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.

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 (version 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. 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

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