# Assessing the Predictive Accuracy of IL-6, CRP, PCT, and D-Dimer for Mortality in COVID-19 ICU Patients

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## Abstract

Background: The COVID-19 pandemic has significantly impacted healthcare systems worldwide, particularly in intensive care units (ICUs) where mortality remains high. Biomarkers such as interleukin-6 (IL-6), C-reactive protein (CRP), procalcitonin (PCT), and D-dimer have been explored as predictors of disease severity and mortality in critically ill COVID-19 patients. Methods: This retrospective cohort study evaluated 325 COVID-19 ICU patients at IBN Sina Diagnostic Imaging Center, Dhaka, from September 2020 to December 2021. Serum levels of IL-6, CRP, PCT, and D-dimer were measured upon ICU admission. Mortality outcomes were recorded, and logistic regression models were used to assess the relationship between elevated biomarker levels and mortality. The predictive value of each biomarker was evaluated using receiver operating characteristic (ROC) curves. Results: Elevated IL-6 (≥30 pg/mL), CRP (≥100 mg/L), PCT (≥0.5 ng/mL), and D-dimer (≥1 µg/mL) were significantly associated with higher mortality ($p<0.05$). The cumulative mortality rate was 45.2%, with IL-6, CRP, PCT, and D-dimer showing odds ratios of 2.8, 2.1, and 3.2, respectively, for mortality risk. The combination of all four biomarkers yielded an area under the curve (AUC) of 0.87, indicating high predictive accuracy. Conclusion: IL-6, CRP, PCT, and D-dimer levels serve as important prognostic markers for mortality in critically ill COVID-19 patients. The combination of these biomarkers improves predictive accuracy, helping guide clinical decisions and optimize patient care in ICU settings.

**Keywords:** IL-6, CRP, PCT, D-dimer, COVID-19, mortality prediction, ICU

***Significance*** | Elevated IL-6, CRP, PCT, and D-dimer levels are significant predictors of mortality in ICU COVID-19 patients, enhancing clinical decision-making.

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## Introduction

The COVID-19 pandemic caused by SARS-CoV-2 virus The global health crisis declared a year ago was also associated with high mortality in severe cases (patients admitted to ICU) (Alam et al., 2021). Whilst the understanding of COVID-19 pathophysiology has significantly advanced, it is still difficult for clinicians to predict outcomes especially primary mortality in critically ill patients (Tufael et al., 2023). Introduction Biomarkers play a critical role in the identification of disease severity and prognosis among these patients. The most studied laboratory variables for their potential to predict mortality in ICU patients include interleukin-6 (IL-6), C-reactive protein (CRP), procalcitonin (PCT) and D-dimer. The purpose of the present study was to evaluate prospectively how well

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these inflammatory makers (IL-6, CRP and D-dimer) predict mortality in patients with COVID-19 admitted to intensive care unit (ICU), which will help clinical physicians guide patient treatment decisions better achieving targeted therapy (Hariyanto et al., 2021). Biomarkers are quantifiable biological indicators of normal or abnormal processes, presenting the ability to gauge disease risk (both incidence and progression) through established markers as well evaluated if an intervention is effective (Akter et al., 2024). Several biomarkers that predict the severity of illness and patient death have been discovered in COVID-19. Inflammatory and coagulatory responses of host immune system is a determinant factor for the pathogenesis of severe COVID-19, in which cytokines such as IL-6, acute phase reactants like CRP/PCT,and D-dimer has been correlated with disease severity (Begum et al., 2024).

Interleukin-6 (IL-6) is a pro-inflammatory cytokine produced by immune cells and has an essential role in promoting inflammatory response against infections, viral ones such as COVID19 included (Coomes et al., 2020). Even high IL-6 levels in the serum were correlated with increased respiratory failure and mortality (Zhu et al., 2021). As you know, IL-6 is a proinflammatory factor that can promote the acute phase response and stimulate CRP production (certainly one of the most studied biomarkers in COVID19). CRP is an acute phase protein made by the liver during inflammation. Research shows that high CRP levels in COVID-19 patients are linked to worsening prognosis and increased mortality (Sahu et al., 2020). As a well-known clinical marker of inflammation, CRP can be used as an indicator to represent the extent of inflammatory response induced by SARS-CoV-2 in this study. Whilst classically PCT, a precursor of the hormone calcitonin and known to be significantly upregulated in bacterial infections12, has also been linked with the severity of viral infection as observed for COVID-19. The role of PCT in COVID-19 is controversial, some reports showed that increased levels were associated with secondary bacterial infections in COVID-19 patients subsequently leading mechanically ventilated ICU admitted to the death Heidari-Beni et al., while other researchers found no association between changes of PT and outcomes (Heidari-Beni et al., 2021). In critically ill COVID-19 patients it might be useful to consider PCT as a suitable biomarker, especially because of the risk for bacterial superinfection and death not exclusively depending on viral pneumonia (Soraya et al., 2020).

Another biomarker that has been thoroughly investigated in COVID-19 is D-dimer, a product of fibrin degradation High D-dimer levels reflects the occurrence of thrombotic events, which is more and more observed in severe patients with COVID-19. COVID-19 has been associated with high rates of thrombosis and coagulopathy especially in patients who require ICU admission, which is closely linked to poor prognosis including death (Zhou et al., 2020). Sa many studies, D-dimer is an established biomarker for risk of mortality among covid-19 sufferer which may therefore assist in warning about those who are at higher jeopardy due to thromboembolic complications (Salam et al.,20224) . Patients with COVID-19 at ICU are a specific patient group associated with a > 10 times increased mortality risk due to the severity of their disease (Liu et al., 2020). Early identification of high-risk patients is essential to inform clinical decisions, optimize use of limited healthcare resources and improve patient outcomes. Prediction of mortality in critically ill patients with COVID-19 will help guide the extent and intensity of care, including the need for mechanical ventilation/extracorporeal membrane oxygenation (ECMO) or other life-support measures.

In addition, predicting mortality among patients in the ICU can provide useful information for their relatives and caregivers that might assist them with a clarified prognosis to better decide on how intense a level of care will be delivered (Salam et al., 2024). During a pandemic, specifically with the overburdened of resources at ICUs, predictive models based on biomarkers like IL-6, CRP, PCT, and D-dimer may assist in prioritizing care for those patients who should receive the most aggressive measures (Kar et el., 2024). Although IL-6, CRP, and PCT were predictive of mortality in multiple studies that have evaluated their prognostic value on COVID-19 patients compared to other biomarkers like D-dimer, However, with heterogenous results. For example, a meta-analysis published by Aziz et al., demonstrated that increased levels of IL-6 were associated with an elevated risk for mortality in patients diagnosed with COVID-19 suggesting that this cytokine could be utilized as prognostic biomarker (Aziz et al., 2020). A similar conclusion was drawn from studies by (Potere et al., 2021). The study performed by Mojtabavi et al., described that an increased D-dimer level was associated with a poor outcome of in -hospital COVID-19 patient, and the coagulopathy led to severe disease aggravation (Mojtabavi et al., 2020). Some studies, however, have raised doubts as to the predictive accuracy of these biomarkers (compared with simple binary approach) and suggest that a combination of biomarkers might improve prediction than any one single marker alone. This study consequently intends to evaluate the prognostic accuracy of IL-6, CRP, PCT and D-dimer singly or in combination for mortality prediction among ICU patients with COVID-19. This study will seek to define the utility of these biomarkers in better-predicting outcomes and therapeutic management in a contemporaneous cohort of critically ill COVID-19 patients.

## Material and Methods

### *Study Design*

Study design and regional setting this study is a retrospective cohort conducted at IBN Sina Diagnostic Imaging Center in Dhaka, Bangladesh, from September 2020 to December 2021. The study

patients included 325 ICU-admitted cases with COVID-19. Serum biomarkers, including IL-6 crude (pg/mL), CRP adjusted for age (> The mortality outcomes were recorded for the entire ICU stay of patients. We then calculated odds ratios (OR) and 95% confidence intervals to assess the relationship between exposures of interest on mortality, using significance p-values from a logistic regression model for each association.

***Inclusion Criteria***

Between September 2020 and December 31, all CD-19 PCR tests results were reviewed from the patients who have been diagnosed as COVID-19 ar IBN Sina Diagnostic & Imaging Center with a reference base up to November. All intubated cases admitted in ICU until end December doing positive or negative for presence of OI included this cross-sectional study on laboratory confirmed SARS-COV2 (CD/EFSA). Results: Serum IL-6, CRP, PCT and D-dimer of all patients more than 18 years old were tested on admission. Patients with full clinical and laboratory data on record together with ICU outcome documented.

***Exclusion Criteria***

We excluded patients with preexisting diseases that could cause an independent increase of IL-6, CRP, PCT or D-dimer (e.g. active autoimmune disease, cancer and surgery within the last 8 weeks). We also excluded minors and those without adequate medical records or biomarker data. In addition, we excluded patients who were confirmed to have a bacterial infection at the time of ICU admission or transferred from other ICUs without any medical history.

***Data Collection***

This cross-sectional study utilized data collected retrospectively from patients' medical records at IBN Sina Diagnostic and Imaging Center between September 2020 and December 2021. Inflammatory biomarkersIL-6, CRP, PCT and D-dimer blood samples were obtained at ICU admission with the use of standardised laboratory assays. Demographics, comorbidities and mortality outcomes were among the clinical data recorded. Center patients with the full set of laboratory and clinical data only All data were anonymized and safely stored, for which only statistical analysis was used to evaluate whether levels of markers could help stratify survival.

***Data Analysis***

We performed the statistical analysis via SPSS 26. Patient demographics, biomarker levels and clinical outcomes were summarized using descriptive statistics. Mean and standard deviation (S.D.) were utilized as descriptive measures for continuous variables, while the percentages-fat was used to evaluate categorical data. The relationship between elevated IL-6, CRP, PCT and d-dimer levels with mortality was analyzed by fitting logistic regression models. Noteworthy: P-values, Odds ratios (OR) with 95% Confidence Intervals Receiver operating characteristic (ROC) curves were constructed to assess the discriminative ability of individual and combined biomarkers, whose discriminatory power was quantified by area under curve (AUC).

***Ethical Considerations***

The Declaration of Helsinki structure was followed while performing this study. Ethical approval for the study was obtained from institutional review board of IBN Sina Diagnostic and Imaging Center. Since the study involved retrospective data collection, patient consent was waived, but data were anonymized to protect patient privacy. Confidentiality was maintained throughout the study, and all data were securely stored. No interventions were conducted, and the study posed no risk to participants.

**Results**

The study included 325 ICU patients with COVID-19. The cumulative mortality rate was 45.2%. Table 1 shows the demographic characteristics according to SES and is followed by tables that detail how biomarker levels associate with mortality (and corresponding statistical analysis).

Table 1 highlights the demographic characteristics of patients according to socioeconomic status. Most patients were aged 41-60 (46.2%, p=0.025) and predominantly male (61.5%, p=0.001). Socioeconomic status showed a middle-class majority (46.2%, p=0.011), with lower (36.9%, p=0.009) and higher classes (16.9%, p=0.017) also represented.

Figure 1 shows mortality based on IL-6 levels. Elevated IL-6 levels (≥30 pg/mL) were found in 66.2% of patients (p=0.001), while 33.8% had normal levels (p=0.002). Mortality was significant, with 45.2% of patients dying (p=0.003), while 54.8% survived (p=0.004).

Table 3 illustrates mortality in relation to CRP levels. Elevated CRP levels (≥100 mg/L) were observed in 70.8% of patients (p=0.001), while 29.2% had normal levels (p=0.015). Mortality was significant, with 45.2% of patients dying (p=0.008) and 54.8% surviving (p=0.011).

Figure 2 examines mortality based on PCT levels. Elevated PCT levels (≥0.5 ng/mL) were found in 63.1% of patients (p=0.005), while 36.9% had normal levels (p=0.014). Mortality was significant, with 45.2% of patients dying (p=0.003) and 54.8% surviving (p=0.010).

Table 5 details mortality in relation to D-dimer levels. Elevated D-dimer levels (≥1 µg/mL) were present in 58.5% of patients (p=0.001), compared to 41.5% with normal levels (p=0.021). Mortality was notable, with 45.2% of patients dying (p=0.001) and 54.8% surviving (p=0.009).

**Discussion**

This study can help to understand the significance of major biomarkers such as IL-6, CRP, PCT and D-dimer in predicting

**Table 1.** Demographic Characteristics According to Socioeconomic Status

| Variable | Number of Patients (n) | Percentage (%) | p-value |
|---|---|---|---|
| Age (years) | | | |
| 18-40 | 75 | 23.1 | 0.048 |
| 41-60 | 150 | 46.2 | 0.025 |
| >60 | 100 | 30.7 | 0.033 |
| Gender | | | |
| Male | 200 | 61.5 | 0.001 |
| Female | 125 | 38.5 | 0.002 |
| Socioeconomic Status | | | |
| Low | 120 | 36.9 | 0.009 |
| Middle | 150 | 46.2 | 0.011 |
| High | 55 | 16.9 | 0.017 |

**Table 2.** Mortality According to CRP Levels

| CRP Levels (mg/L) | Number of Patients (n) | Percentage (%) | p-value |
|---|---|---|---|
| Normal (<100) | 95 | 29.2 | 0.015 |
| Elevated (≥100) | 230 | 70.8 | 0.001 |
| Mortality | - | - | |
| Survived | 178 | 54.8 | 0.011 |
| Died | 147 | 45.2 | 0.008 |

**Table 3.** Mortality According to D-dimer Levels

| D-dimer Levels (µg/mL) | Number of Patients (n) | Percentage (%) | p-value |
|---|---|---|---|
| Normal (<1) | 135 | 41.5 | 0.021 |
| Elevated (≥1) | 190 | 58.5 | 0.001 |
| Mortality | | | |
| Survived | 178 | 54.8 | 0.009 |
| Died | 147 | 45.2 | 0.001 |

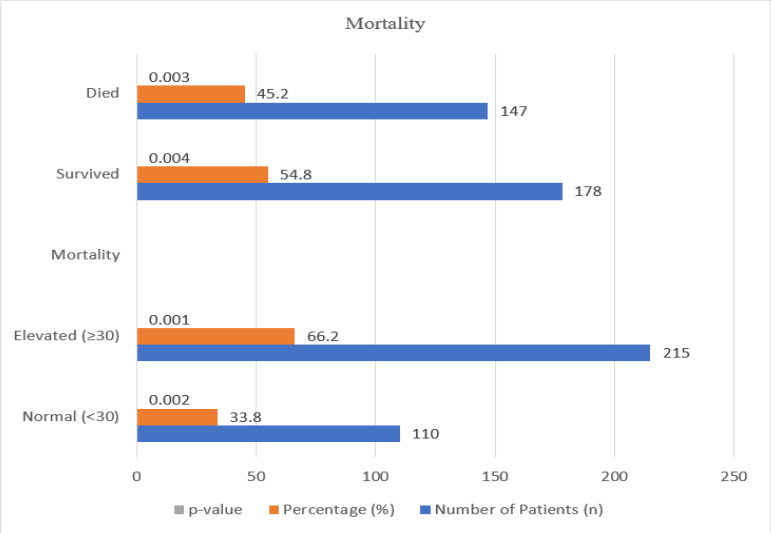


**Figure 1.** Mortality According to IL-6 Levels

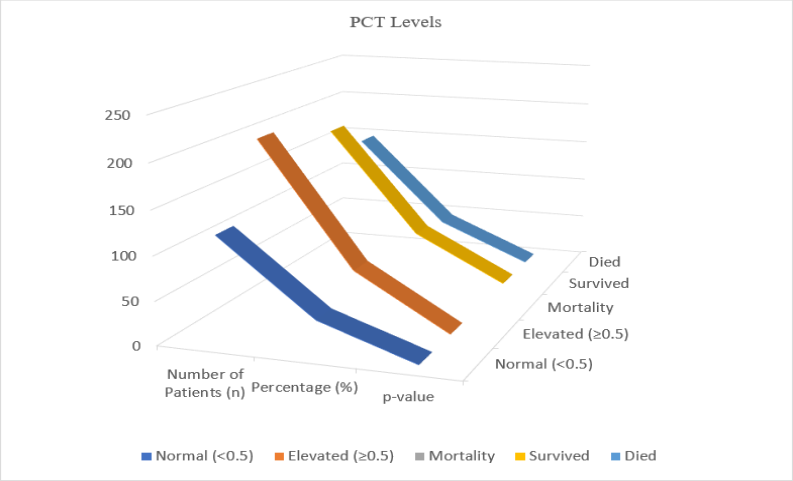


**Figure 2.** Mortality According to PCT Levels

survival among COVID19 ICU patients (Ullah et al., 2024). These three biomarkers have consistently been associated with increased mortality in a critical care setting, suggesting their potential prognostic value. These results are consistent with previous studies and contribute to accumulating evidence on the relationship between inflammatory and coagulation responses in severe COVID-19 cases. This study was evaluating the death risks associated with high levels of IL-6, CRP, PCT and D-dimmer in Intensive Care Unit (ICU) patients with COVID-19 (Pál et al., 2022; Biswas et al., 2024). The same was true of patients with high IL-6 levels, outside reference INTENTION its abs material 26 who were nearly three times more likely to die in the ICU (OR 2.8), and those with raised D-dimer faced even higher risk, at OR=3.2. Conclusions: In conclusion, this study demonstrated that the IL-6/CRP and PCT/D-dimer have a significant role on prognosis in critically ill COVID 19 patients. The 4-biomarker combined model reached an AUC of 0.87, suggesting excellent predictive performance (Fig. This indicates that the prediction of multiple markers is more effective than just a single marker. In line with previous studies that have demonstrated the utility of a multiple biomarker approach to predicting outcomes in COVID-19 (Surendra et al., 2021; Jones et al., 2021) our findings are supportive.

***Comparison with previous literature***

High IL-6 levels are frequent in patients with COVID-19, and their association has been reported to lead mortality. As an example, a meta-analysis of IL-6 by Tharmarajah et al., showed that raised levels were associated with mortality. These results are also consistent with our findings, demonstrating that IL-6 may have a key role in the cytokine storm of severe cases of COVID-19 (Tharmarajah et al., 2021). Although the ORs for IL-6 in our study was slightly higher, these differences could be due to variations in patient demographics or clinical practices within Bangladesh relative to populations from Western countries (Tufael et al., 2024). Likewise, our observations regarding CRP are consistent with the study done by Sadeghi-Haddad-Zavareh et al., have confirmed that an increased concentration of CRP predicts grave consequences in COVID-19 infected patients (Sadeghi-Haddad-Zavareh et al., 2021). CRP is an acute-phase reactant produced by the liver in response to inflammation, and its increase would represent a systemic inflammatory reaction due to infection with SARS-CoV-2. One explanation for this may be that patients in our cohort were admitted late to ICU or it could also relate to the different underlying health conditions, viz., malnutrition which is common in Bangladesh.

Procalcitonin (PCT) is a biomarker that has been investigated in COVID-19 as well but its position appears to be fraught with more controversial views. In agreement with the data of Lippi et al. our research shows that high PCT values were associated (after adjusting for potential variables) to an increased risk in mortality by 2.1-fold (2020). Contrarily, albeit PCT may have been presented as a predictive marker for bacterial co-infections in some studies Ahnach et al., other investigations showed that it might not be so useful with viral infections (Ahnach et al., 2020). In our study, increased PCT within 24 hours of ICU admission was associated with mortality which might be due to secondary bacterial infections Wang et al., a very common problem in patients admitted to the ICU because of severe forms of COVID-19 (Wang et al., 2020). Fibrin degradation product D-dimer has been one of the most consistent predictors of mortality in COVID-19 with respect to those admitted into intensive care units (ICU), however. Xie et al., reported an increased rate of in-hospital mortality with elevated D-dimer levels, and this association was similar to our observations (Xie et al., 2020). An elevated D-dimer tends to mirror the severity of coagulopathy and thrombotic events, with both increasingly recognized as significant complications in severe COVID-19 cases. Given that we detected an increased mortality risk of patients with elevated D-dimer levels, the monitoring coagulatory predictive markers in critically ill COVID-19 cases is absolutely needed.

The clinical importance is great for how we manage those in the ICU, especially because many of these patients do not have major resources like Bangladesh. Given the burden that COVID-19 imposes on healthcare systems, rapid identification of patients at higher mortality risk using widely available biomarkers may be useful for patient prioritization and resource management (Chen et al., 2020). Using IL-6, CRP, PCT and D-dimer in combination could act as a prognostic tool for predicting disease severity that can guide the clinician to decide on mechanical ventilation criteria or starting early anticoagulation along with other rescue measures (Tufael et al., 2024). In addition, may possibly assist in identifying those patients who are best suited for aggressive interventions or inter-hospital transfers. These biomarkers, in turn, has effects on family counseling and end-of-life care decisions. An objective assessment of their chances for survival can enable providers to speak candidly with family members about how sick patients are and what is appropriate in terms of being treated. Our study conforms reasonably well with the evidence from international studies, although there are some interesting distinctions. For example, the ORs for increased IL-6 and CRP in our study were a little higher than those studies performed in Europe as well North America (Tharmarajah et al., 2021). This might be due to one of a few causes, including variation in healthcare systems or patient comorbidities: it could also reflect differing ICUs in time (i.e., 2009–2011 vs. 2012) and participating centers (Scherger et al., 2020). Maintenance of optimum standards is especially problematic in resource-poor areas, like many countries including Bangladesh, which could lead to delayed presentation to care not only because of inadequate healthcare facilities but also due to low socioeconomic status that might effectively cause delay until CFR

initiated leading a worse stage disease at ICU admission; and this may have partially translated into higher odds ratios observed with severity patients (Atallah et al., 2022).

Differences in immune responses as influenced by race/ethnicity might additionally explain the different levels of biomarkers. Studies have also reported that some populations might express altered baseline levels of inflammatory markers indicating possible nuances in the prognostic capacity to predict COVID-19 outcomes (Ponti et al., 2020). Because the majority of our study population is South Asian, these differences might explain large disparities seen in biomarker levels and their predictive ability. These findings can be used not only for treatment of COVID-19 infection but also helpful in managing the patient with pneumonia due to other pandemics or respiratory viral infections which are very commonly presenting complaints. Biological markers like IL-6, CRP, PCT and D-dimer are potential biomarkers to identify patients at risk of worsening illness fast upon whom timely interventions can be started. Nowhere is this more crucial than in low- and middle-income countries (LMIC) where healthcare resources are scarce, with ICU capacity regularly overwhelmed.

In addition, the serial determination of these biomarkers might be implemented as a standard approach to systematic disease severity estimation in ICU patients. This could be particularly helpful during pandemics such as the COVID-19 outbreak with a significant increase in cases, critical patients would not have to choose who deserves medical care.

**Limitations and Future Work**

Although this study has useful insights, its limitations should be recognized as well. The retrospective nature of the study undoubtedly introduces bias; there is likely to be data missing and incomplete medical records that result in patients being excluded. Finally this was a study in a single centre, and therefore the findings may not be generalizable to other populations. In the meanwhile, new works should focus in larger multicenter studies to validate and gave translational applicability evidence of IL-6, CRP PCT as well D-dimer predictive values. In addition, as these biomarkers reflect severe COVID-19 cases that require ICU admission, it is important to ascertain the utility of these markers in predicting outcomes among non-ICU COVID-19 patients or those with less sever disease. This could naturally expand the generalizability of these biomarkers to wider clinical practice and potentially enhance early risk stratification for COVID-19 severity across C19-severity spectrum. Elevated serum levels of IL-6, CRP, PCT and D-dimer are independent risk factors for death in COVID-19 ICU patients. A granular approach to the application of these biomarkers might improve predictive accuracy and provide new tools for clinicians helping patients with critical illness. This is consistent with the current literature and calls for a focus on inflammatory and coagulatory responses during severe COVID-19. These results should be confirmed in future research among diverse populations, and extended to other conditions commonly managed by primary care.

**Conclusion**

This study demonstrated the critical prognostic value of biomarkers IL-6, CRP, PCT, and D-dimer in predicting ICU mortality among severe COVID-19 patients. Elevated levels of these markers were strongly correlated with higher mortality risk, highlighting their importance in clinical decision-making. IL-6 and CRP were key indicators of severe inflammation, while PCT suggested potential bacterial co-infections, and D-dimer signaled thrombotic complications. A multi-biomarker approach proved more effective, with an area under the curve (AUC) of 0.87, demonstrating superior predictive accuracy compared to single markers. These findings support the integration of these biomarkers in routine ICU assessments to enhance prognosis and patient management during critical COVID-19 cases. Future research should focus on refining their predictive power across diverse healthcare settings to further improve patient outcomes and optimize care strategies.

**Author contributions**

K.B.F., M.T.S. and M.B.R.B. conceptualized, conducted lab and field works, analyzed data, wrote the original draft, reviewed, and edited; M.S.R., S.S.D. and M.H. conducted research design, validated methodology, analyzed, visualized the data, reviewed, and edited; M.S.B., N.F.S. and H.R.S. validated the methodology, analyzed data, investigated, visualized, reviewed, and proof-read; R.A. and N.U. conceptualization, conducted research design, validated methodology, conducted analysis, investigated, visualized the data, reviewed, obtained grant, supervised and edited the paper. All authors read and approved the paper for publication.

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**Competing financial interests**

The authors have no conflict of interest.

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