Prospective study of coagulation parameters in septicemic patients

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ABSTRACT

Background and objectives. Sepsis is a critical clinical syndrome characterized by a systemic host response to infection, often leading to organ dysfunction and mortality. The association between early onset coagulopathy and mortality risk in septicemic patients remains an area of active investigation. This study aims to assess the association between early onset coagulopathy and increased mortality risk in septicemic patients. It also seeks to explore the role of procalcitonin (PCT) levels and demographic factors in the prognosis of septicemia.

Material and methods. A cross-sectional study was conducted at Saveetha Medical College and Hospital, including 240 subjects who met the inclusion criteria. Patients were evaluated for the presence of coagulopathy (assessed by platelet count, INR, and aPTT values) and their PCT levels within 48 hours of admission. Data on demographic characteristics, underlying illnesses, and 28-day mortality were collected and analyzed.

Results. The study population had a male preponderance (53.3%) with a mean age of 56.27 years. Diabetes mellitus was the most common underlying illness (32.5%). Coagulopathy was observed in 52.5% of patients, with thrombocytopenia and deranged INR and aPTT being significant indicators. Patients with life-threatening thrombocytopenia, severe PT-INR, and aPTT derangements showed high mortality rates (100%, 92.4%, and 90%-95.6% respectively). Mortality was significantly associated with coagulopathy and elevated PCT levels (>10.0 ng/ml), with 41.7% of subjects dying within 28 days of admission.

Conclusions. Early onset coagulopathy is significantly associated with increased mortality in septicemic patients, highlighting the importance of coagulation parameters and PCT levels in predicting outcomes indicating prompt recognition and management of coagulopathy in septicemia, especially in younger patients and those with elevated PCT levels.

Keywords: thrombocytopenia, septicemic, coagulopathy, mortality

INTRODUCTION

Sepsis is widely recognized as a clinical syndrome, resulting from an overwhelming systemic host response to infection [1]. The key clinical manifestations of sepsis are not caused directly by the invading pathogens; rather, the hypotension, coagulopathy, and multisystem organ dysfunction that characterize severe sepsis are predominantly a result of dysregulation of host-derived mediators of inflammation [2].

Coagulopathy is a condition in which the blood’s ability to clot the blood is impaired [3]. However, for some clinicians, the term also covers thrombotic states, and because of the complexity of hemostatic pathways, the two conditions can co-exist simultaneously. Derangement of coagulation parameters is one of the common laboratory findings in septicemic patients. They can be associated and more pronounced in simultaneous co-morbid illnesses like chronic liver
disease, renal disease and other known causes of thrombocytopenia. Sepsis is the most common cause of death among hospitalized patients in non-cardiac intensive care units and has been investigated in a lot of preclinical and clinical research [4]. Tremendous progress has been made in understanding the complex triad of infection, inflammation, and coagulation during sepsis. New insights into the vital role of the balance between procoagulant, anticoagulant, and fibrinolytic pathways during sepsis and the role of the endothelium herein continue to challenge our understanding of the sepsis syndrome. In the last years, research in this field has expanded its focus, now also covering microparticles, apoptosis, and platelets [5]. Despite continuing advances in intensive care medicine, severe sepsis and septic shock are currently among the most common causes of morbidity and mortality in intensive care. Moreover, the incidence of severe sepsis and septic shock has increased with ageing of the population over the past decade [6, 7]. Within the last decade, several trials and protocols have focused on establishing better measures for early diagnosis, effective management and prevention of potential complications in sepsis. Therapeutic measures with considerable positive impacts have been largely emphasized; however, assessing the prognosis of sepsis remains difficult. This study aims to assess the association between early onset coagulopathy and increased mortality risk in septicemic patients also help to assess early onset coagulopathy as a predictor of outcome in septicemic patients.

**MATERIALS AND METHODS**

This Prospective cross sectional observational study was conducted on 240 Septicemia patients admitted in Intensive care unit (ICU) at tertiary care Saveetha medical college and hospital. **Inclusion criteria:** Patients with suspected or documented infection (via culture reports), fulfilling the criteria of SIRS. **Exclusion criteria:** Patients less than 16 years of age, Patients admitted with Trauma, surgical patients, Pregnancy and Patients not willing for consent. **Study method:** Case selection was done on the basis of inclusion and exclusion criteria. Risk factors were noted as: Diabetes Mellitus, Hypertension, Chronic Kidney Disease (CKD), Chronic Liver Disease (CLD), Malignancy (on treatment: either chemotherapy/radiotherapy except palliative care), HIV infection and Ischemic Heart Disease (IHD). Further investigation results were noted as follows: Coagulation parameters within 48 hours of admission: Platelet count, Prothrombin time – International Normalised Ratio (PT-INR), Activated partial thromboplastin time (aPTT), other tests e.g. Procalcitonin (PCT) (if done as per Clinician discretion).

Data obtained was categorized as follows [8,9]:
1. Platelet count: More than 1, 50,000: No thrombocytopenia, 1,50,000 - 75,000: Mild thrombocytopenia, 75,000 - 50,000: Moderate thrombocytopenia, 50,000 - 25,000: Severe thrombocytopenia. Less than 25,000: Life-threatening.
2. International Normalized Ratio (INR): Normal, More than 1-1.5 times Upper Limit of Normal: Grade I (Mild derangement), More than 1.5-2 times Upper Limit of Normal: Grade II (Moderate), More than 2 times Upper Limit of Normal: Grade III (Severe)
3. Activated Partial Thromboplastin Time (aPTT): Normal, More than 1-1.5 times Upper Limit of Normal: Grade I (Mild derangement), More than 1.5-2 times Upper Limit of Normal: Grade II (Moderate), More than 2 times Upper Limit of Normal: Grade III (Severe)

Serum Procalcitonin [10]:
- PCT < 0.5 ng/ml: Local bacterial infection possible, systemic infection (sepsis) unlikely. PCT > 0.5 & < 2 ng/ml: Suggests systemic infection (sepsis).
- PCT > 2 & < 10 ng/ml: Suggests severe sepsis.
- PCT > 10 ng/ml: Suggests almost exclusively septic shock

Coagulopathy was defined as [3]:
- Platelet count < 1,50,000
- PT – INR > 1.5 times the upper limit of normal
- aPTT > 1.5 times the upper limit of normal.

Patient was considered to have coagulopathy even if only one of the above parameters were deranged.

Early-onset coagulopathy: Patients admitted with septicemia having coagulation parameters deranged within 48 hrs of admission were considered to have early-onset coagulopathy in our study.

**Statistical methods**

Statistical analysis was conducted using SPSS version 20, summarizing quantitative data with mean ± SD and qualitative data with percentages. Significance was set at P < 0.05. Student’s t-test and Chi-square or Fisher’s exact test assessed differences and associations. Multiple logistic regression analyzed thrombocytopenia’s impact on mortality and its risk factors, reporting odds ratios (OR) and 95% confidence intervals (CI).

**RESULTS**

In our study, Diabetes Mellitus was observed to be the most common underlying illness present in 32.5%
cases followed by HTN in 19.6%, CLD in 15.0%, IHD in 12.5% and Malignancy in 11.7%. Chronic Kidney Disease (CKD) was present in 6.7% cases and HIV in 4.6% cases (Table 1).

**TABLE 1.** Demographic variables of patients

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>Number of patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 30</td>
<td>2</td>
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</tr>
<tr>
<td>31 - 40</td>
<td>16</td>
<td>6.7</td>
</tr>
<tr>
<td>41 - 50</td>
<td>13</td>
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<tr>
<td>51 - 60</td>
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<td>14.6</td>
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<td>61 - 70</td>
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<td>71 - 80</td>
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<td>81 - 90</td>
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<tr>
<td>&gt;90</td>
<td>17</td>
<td>7.1</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>128</td>
<td>53.3</td>
</tr>
<tr>
<td>Female</td>
<td>112</td>
<td>46.7</td>
</tr>
<tr>
<td>Chronic Illness</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>78</td>
<td>32.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>47</td>
<td>19.6</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>16</td>
<td>6.7</td>
</tr>
<tr>
<td>Chronic Liver Disease</td>
<td>36</td>
<td>15.0</td>
</tr>
<tr>
<td>Malignancy</td>
<td>28</td>
<td>11.7</td>
</tr>
<tr>
<td>HIV</td>
<td>11</td>
<td>4.6</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>30</td>
<td>12.5</td>
</tr>
<tr>
<td>Total</td>
<td>240</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2 shows 55.8 % (134/240) of septicemic patients not having thrombocytopenia as compared to 20% (48/240) patients having mild thrombocytopenia, 5.8% moderate (14/240), 12.1% (29/240) severe and 6.3% (15/240) having life threatening thrombocytopenia. INR was deranged in 66.7% septicemic patients, 33% (80/240) study subjects had normal PT-INR levels whereas 29.6% (71/240) had mild derangement, 15% (36/240) moderate and 22.1% (53/240) had severe derangement in PT-INR value. 37.1% (89/240) study subjects had normal aPTT value whereas 35.4% (85/240) study subjects had mild aPTT derangement, 19% (46/240) moderate and 8.3 % (20/240) had severe derangement in aPTT value.

As shown in Table 3, coagulopathy was seen in 52.5% (126/240) study subjects and was absent in 47.5% (114/240) study subjects. Thrombocytopenia related coagulopathy was seen in 44.1% (106/240) patients; PT-INR derangement related coagulopathy was seen in 37.08% (89/240) patients and aPTT derangement related coagulopathy was observed in 27.5% (66/240) patients.

Table 4 shows, mortality was observed less i.e. 14.1% (19/134) with patients having normal platelet counts whereas 54.16% (26/48) mortality was seen in mild thrombocytopenia, 92.85% (13/14) in moderate thrombocytopenia, 93.1% (27/29) in severe thrombocytopenia and 100% (15/15) mortality in life threatening thrombocytopenia. This was seen to be statistically significant by using Fisher’s exact test (P < 0.05). 3.7% (3/80) mortality was seen in patients with normal PT-INR whereas 22.53% (16/71) in mild PT-INR derangement, 88.8% (32/36) in moderate and 92.4% (49/53) in severe PT-INR derangement. This association was observed to be statistically significant with Fisher’s exact test (P < 0.05).
Table 5 shows analysis of 28-day mortality in relation to individual coagulation parameters fitting in coagulopathy. 77.77% (98/126) mortality was seen in patients with coagulopathy whereas only 1.7% (2/114) in patients without coagulopathy. Association was seen to be statistically significant by using Fisher's exact test (P<0.05). Mortality in patients having thrombocytopenia related coagulopathy was 76.41% (81/106), mortality in patients with PT-INR derangement related coagulopathy was 91% (81/89) and mortality in patients with aPTT derangement related coagulopathy was 93.9% (62/66). Significant statistical association was seen by using Fisher's exact test (p<0.05) between 28-day mortality and coagulopathy.

Table 6 and 7 shows analysis of 28-day mortality with PCT level in study subjects. PCT was done in 42 study subjects as per clinician discretion. No mortality i.e. 0% (0/11) was seen in subjects with normal PCT levels whereas 100% (18/18) mortality was seen with high PCT levels (>10.0 ng/ml). This association between 28-day mortality with PCT level was shown to be statistically significant with Fisher's exact test (P < 0.05). Out of 42 patients in whom PCT was done, Coagulopathy was absent i.e. 0% (0/11) in subjects with
normal PCT levels; however, prevalence of coagulopathy increased with increase in PCT levels to 100% (18/18) in subjects having PCT > 10.0 ng/mL. This association was shown to be statistically significant with Fisher’s exact test (P<0.05).

### DISCUSSION

In the present study, mean age of the patients was 56.27 years (19-101, SD= +/- 15.05). This was in concurrence with the mean age in a study by Sekhon and group [22] in 2013, which was 59 years, SD +/- 16. Jeganathan and group [12] in a multicenter prospective observational study conducted in India in 2010 observed that the mean age of study population was 58.17 years (SD 18.66). In a study conducted by Angus and group [13] in 2001, mean age was seen to be 63 years. Out of the 240 study subjects, 53.3% (128/240) were males and 46.7% (112/240) were females. Our study showed male preponderance over females. Similar sex distribution was seen in a study by Padkin and group in 2003, showing male preponderance (58.8%) over females [14]. Jeganathan and group in a multicenter prospective observational study in 2010 observed that out of the 5,478 admissions, 57.71% were males. In a study conducted by Martin and group [7] in 2003, male population outnumbered female population.

**Diabetes Mellitus:** In our study, 32.5% (78/240) subjects suffered from diabetes mellitus, whereas 67.5% (162/240) were non-diabetic. In a study conducted by Wang and group [15] in 2012, out of the 30,239 participants included in study, 47% had Diabetes Mellitus. Prevalence of Diabetes Mellitus in our study was relatively high as compared to a study by Stegenga and group [16] in 2010, which included 830 subjects, wherein 22.7% subjects were diabetic. In a study conducted by Esper and group [17] in 2009, out of the 12.5 million cases of sepsis enrolled in study, 17% had Diabetes Mellitus.

Hypertension accounted for 19.6% (47/240) of study subjects in our study. On the contrary, hypertension was seen in only 3.76 per 100-people in a study which included 30,239 participants and was conducted by Wang [15] in 2012. This difference in prevalence of hypertension could be due to sample size bias as our study included a small size i.e. 240 subjects as compared to above mentioned study which included 30, 239 subjects. CKD was seen in 6.7% (16/240) subjects in our study. This was in concurrence with study by Wang et al.15 in 2012, wherein prevalence of CKD was 5.34 per 100 participants.

Malignancy was associated with sepsis in 11.7% (28/240) patients in our study. This was similar to findings in a study conducted by Davai and group [18] in 2006 where Cancer was one of the common comorbid medical conditions in patients with sepsis, reported to occur in 16.8% of US sepsis patients and in 16.7% of European and Canadian sepsis patients. Williams and group [19] in their study in 2004, found that out of all the malignant cases included, severe sepsis was seen in 4.9% cases.

**Ischemic heart disease:** IHD was observed in 12.5% (30/240) study subjects in our study. This was double of what was observed in study conducted by Wang and group [15] where IHD was an underlying illness in sepsis in 6% cases. The above difference could be because of the sample size bias as our study had smaller sample size compared to the study conducted by Wang and group which included 30,239 participants.

The unfavourable impact of cirrhosis on outcomes of sepsis has been well studied in recent past. In our study, 15% (36/240) of subjects was found to have associated risk factor as CLD. In a retrospective study by Sauneuf and group [20] in 2013, with a study period of 14-years, incidence of sepsis in cirrhotic patients was found to be 5.5% (89/1632). Foreman and group [21] in their study observed sepsis to be present in 4.9% of the cirrhotic patients i.e. 79,800 out of 1.7 million hospitalizations studied in 2003.

The epidemiology of sepsis in patients with HIV is changing significantly with advancements in highly active antiretroviral therapy (HAART) and Pneumocystis jirovecii prophylaxis. 4.6% (11/240) of the total patients included in our study had HIV as an underlying illness. Data from a single center study in 2012 by Greenberg and group [22] in the United States found approximately 13.7% HIV-positive patients among all ICU admissions, with an overall in-hospital mortality of 42%.
Most critically ill patients with a systemic inflammatory response have coagulation disorders and thrombocytopenia is the most frequent finding [23, 24]. In our study, we observed that 44.2% (106/240) subjects developed thrombocytopenia within 48 hrs of admission whereas 55.8% (134/240) did not develop thrombocytopenia. 20% patients developed mild thrombocytopenia, 5.8% developed moderate thrombocytopenia, 12.1% had severe thrombocytopenia and 6.3% developed life threatening thrombocytopenia. This was in concurrence with a retrospective analysis by Venkata and group [25] in 2013, where thrombocytopenia occurred in 47.6% of the sepsis-related 304 cases admitted in ICU. In a prospective observational study by Boechat and group [26] in 2012, 60.7% patients admitted with sepsis i.e. 34 out of 56 developed thrombocytopenia. In a study by Levi [23] thrombocytopenia <1,00,000 was seen in 20-25% cases and 12-15% cases had thrombocytopenia <50,000.

Sepsis leads to deranged coagulation, ranging from mild alterations up to severe DIC. In our study, 33% (80/240) study subjects had normal PT-INR levels whereas 29.6% (71/240) had mild derangement, 15% (36/240) moderate and 22.1% (53/240) had severe derangement in PT-INR value. We also saw that 37.1% (89/240) study subjects had normal aPTT value whereas 35.4% (85/240) study subjects had mild aPTT derangement, 19% (46/240) moderate and 8.3% (20/240) had severe derangement in aPTT value. Similar findings were seen in a study of 235 patients by Chakraverty and group [27] wherein INR was deranged in 66% cases. Macleod [28] in a prospective study from a trauma registry cohort which included 20,103 patients observed that early derangements in PT-INR and aPTT were both associated with poorer outcomes and had statistically significant correlation with mortality. However, the study was conducted on trauma patients who formed one of the exclusion criteria of our study.

Coagulopathy in relation to individual coagulation parameters: In our study, thrombocytopenia related coagulopathy was seen in 44.1% (106/240) patients; PT-INR derangement related coagulopathy was seen in 37.08% (89/240) patients and aPTT derangement related coagulopathy was observed in 27.5% (66/240) patients. Overall, prevalence of coagulopathy in our study was 52.5% (126/240) and was absent in 47.5% (114/240) study subjects.

In our study, mortality was seen to be less with patients having normal platelet counts; however mortality increased with increase in severity of thrombocytopenia. This was seen to be statistically significant by using Fisher’s exact test (P < 0.05). Mortality was less i.e. 14.1% (19/134) with patients having normal platelet counts whereas 54.16% (26/48) mortality was seen in mild thrombocytopenia, 92.85% (13/14) in moderate thrombocytopenia, 93.1% (27/29) in severe thrombocytopenia and 100% (15/15) mortality in life threatening thrombocytopenia. Sharma et al. [29] in their study of 69 patients with septic shock in 2007, observed that incidence of thrombocytopenia in their study was 55% and platelet count was found to be predictor of increased mortality.

**PT-INR and aPTT:** Less mortality was seen with normal PT-INR and aPTT values; however mortality increased with prolongation in PT-INR and aPTT values. This association between 28-day mortality with deranged INR or aPTT was shown to be statistically significant with Fisher’s exact test (p<0.05). Chakraverty et al. [27] observed that PT-INR derangement was associated with poorer outcome in critically ill patients. Macleod et al. [28] in a prospective study in 2003 from a trauma registry cohort which included 20,103 patients observed that early derangements in PT-INR and aPTT were both associated with poorer outcomes and had statistically significant correlation with mortality. However, the study was conducted on trauma patients who formed one of the exclusion criteria of our study.

Thrombocytopenia related coagulopathy was seen in 106 patients, out of which mortality was seen in 81 cases and survival in 25 cases. Remaining 134 patients had normal platelet counts out of which 115 survived and 19 died. Mortality rate amongst thrombocytopenic patients was 76.4% (81/106) and amongst non-thrombocytopenic patients was 14.1% (19/134). This was in contrast to the observation made by Venkata and group [25] in a retrospective analysis in 2013, which included 304 patients where no significant mortality difference in thrombocytopenic (32.4%) and non-thrombocytopenic patients (24.5%) was seen. Prolonged PT-INR related coagulopathy was seen in 89 cases out of which mortality was seen in 91% (81/89) cases. Prolonged aPTT related coagulopathy was seen in 66 patients out of which mortality was present in 93.9% cases (62/66). Significant statistical association was seen by using Fisher’s exact test (p<0.05) between 28-day mortality and coagulopathy mentioned above. Overall, out of 240 subjects enrolled in our study, 52.5% (126/240) had coagulopathy of which mortality was seen in 77.77% (98/126) cases; 47.5% (114/240) subjects had coagulation parameters in normal limits of which mortality was seen in 1.7% (2/114) cases. Significant statistical association was seen by using Fisher’s exact test (p<0.05) between 28-day mortality and coagulopathy as discussed above. In our study, overall mortality rate was 41.7% (100/240) and survival rate was 58.3% (140/240).

Jeganathan et al. in a multicenter prospective observational study conducted in India in 2010, which included 5,478 admissions, observed that the mortality rate among admissions related to sepsis was 59.26%. Gaieski et al. [30] in 2013 using a nationally representative sample from four previously published studies observed that in-hospital mortality across the 6-year period (2004-2009) had decreased...
from 35.2% to 25.6%. In a retrospective observational study by Angus [13] in 2001, a study population of 1,92,980 subjects with severe sepsis were enrolled and observed mortality was found to be 28.1%. Mortality rates seen in our study was considerably higher as compared to western literature. This difference was possibly due to sample size bias and differences in management practices with western world. Our study when compared to the study by Jeganathan et al.12 as mentioned above, both showed higher mortality rates. This was mostly because both the studies were conducted in Indian setting.

Measurement of procalcitonin can be used as a marker of severe sepsis caused by bacteria and generally grades well with the degree of sepsis [31, 32]. In our study, PCT was done in 42 subjects, at clinician’s discretion, wherein 26.2% (11/42) had normal PCT levels, 9.5% had levels between 0.51 – 2.0 ng/ml (suggestive of sepsis), 21.4% had levels between 2.01 – 9.99 ng/ml (suggestive of severe sepsis) and 42.9% had levels >10 ng/ml (suggests septic shock). Observed mortality rate increased with higher PCT values such that no mortality 0% (0/29) was seen in subjects with normal PCT values and 100% (18/18) mortality was seen in subjects with values >10 ng/ml .Thus, high PCT level was associated with increased mortality risk. Relationship between 28-day mortality and PCT level was found to be statistically significant by Fisher’s exact test (P<0.05). Similar findings were observed in 2015 by Li and group [33] in a retrospective analysis of 115 patients admitted in ICU with ventilator associated pneumonia where Serum procalcitonin was found to be an independent prognostic biomarker of mortality in critically ill patients. Sharma and group [29] in 2014 observed similar relationship between high PCT level and increased mortality risk. However, our observation was in contrast to a prospective observational study by Sudhir et al. [34] in 2011 wherein no significant association was seen between PCT level and associated mortality, possibly attributable to sample size differences in both the studies. Also, relationship between PCT and coagulopathy was assessed in our study. High PCT was associated with increased coagulopathy risk. Out of 42 patients in whom PCT was done, Coagulopathy was absent i.e. 0% (0/11) in subjects with normal PCT levels; however, prevalence of coagulopathy increased with increase in PCT levels to 100 % (18/18) in subjects having PCT > 10.0 ng/ml. This relationship was observed to be statistically significant by using Fisher’s exact test (<0.05). However, our observation could not be compared to other studies in view of paucity of literature.

CONCLUSION

Early onset coagulopathy is significantly associated with increased mortality risk in septicemic patients. Septicemic patients of relatively younger age having coagulopathy have increased mortality rate. Role of PCT in septicemic patients might have considerable prognostic significance. PCT value correlates with coagulopathy in septicemic patients enrolled in our study. Septicemia/Sepsis has a more significant predominance in male population over females and underlying medical illnesses have a remarkable impact on the mortality outcome.

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No conflict of interest to declare.

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Validation: Dr Gowri Shankar; N.Krishna Geetha;
Formal analysis, N.Krishna Geetha; K.I.S.N Vaishnavi
Investigation: N.Krishna Geetha; K.I.S.N Vaishnavi
Resources: Dr. Kakumani Jagadeswar
Data curation: K.I.S.N Vaishnavi; Dr. Gowri Shankar;
Writing—original draft preparation: N. Krishna Geetha; K.I.S.N Vaishnavi
Writing—review and editing: N. Krishna Geetha;
K.I.S.N. Vaishnavi; Dr. Kakumani Jagadeswar
Visualization: Dr. Gowri Shankar; Dr. Kakumani Jagadeswar
Project administration: Dr. Kakumani Jagadeswar

All authors have read and agreed to the published version of the manuscript.

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