Neutrophil Lymphocyte Ratio can preempt Development of Sepsis after Adult Living Donor Liver Transplantation

AUTHORS

Shashwat Sarin¹, Viniyendra Pamecha², Piyush Kumar Sinha³, Nilesh Patil⁴, Nihar Mahapatra⁵

¹ Senior Resident, Department of Liver Transplant and Hepato Pancreato Biliary Surgery, Institute of Liver and Biliary Sciences, New Delhi, India

shashwat.sarin@gmail.com

² Professor, Head of Department, Liver Transplant and Hepato Pancreato Biliary Surgery, Institute of Liver and Biliary Sciences, New Delhi, India

viniyendra@yahoo.co.uk

+91 9540946803

CORRESPONDING AUTHOR

³ Assistant Professor, Department of Liver Transplant and Hepato Pancreato Biliary Surgery, Institute of Liver and Biliary Sciences, New Delhi, India
piyushkumarsinha@gmail.com

+91 9920 69007

4 Assistant Professor, Department of Liver Transplant and Hepato Pancreato Biliary Surgery, Institute of Liver and Biliary Sciences, New Delhi, India

dr.nils.p@gmail.com

+91 99115 94576

5 Assistant Professor, Department of Liver Transplant and Hepato Pancreato Biliary Surgery, Institute of Liver and Biliary Sciences, New Delhi, India

nihar0310@gmail.com

+91 95409 46843

KEYWORDS

Infection, Biomarker, Detection, NLR, Sepsis, Early Diagnosis, Outcomes, Living donor liver transplant, Neutrophil lymphocyte ratio
FOOTNOTE PAGE

ABBREVIATIONS.

ACLF – Acute on Chronic Liver Failure
AUC – Area Under Curve
CLD – Chronic Liver Disease
CRP – C Reactive Protein
GRWR – Graft Recipient Weight Ratio
LDLT – Living Donor Liver Transplantation
MELD Na – Model for End stage Liver Disease Sodium
MHV – Middle hepatic vein
NLR – Neutrophil Lymphocyte Ratio
POD – Post operative Day
ROC – Receiver Operator Curve
SIRS – Systemic Inflammatory Response Syndrome
TLC – Total Leukocyte Count

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CORRESPONDING AUTHOR

Dr. Viniyendra Pamecha
Professor, Head of Department, Liver Transplant and Hepato Pancreato Biliary Surgery,
Institute of Liver and Biliary Sciences, New Delhi, India
viniyendra@yahoo.co.uk
+91 9540946803
ABSTRACT

Background: Development of sepsis is a major contributor to poor outcomes after liver transplant. The neutrophil-lymphocyte ratio (NLR) is an easily calculable inflammatory biomarker. We aim to utilize NLR to diagnose and predict the onset of sepsis in patients undergoing living donor liver transplant (LDLT).

Materials and methods: Analysis of the perioperative course of 314 consecutive adult patients who underwent elective ABO compatible LDLT was done. Patients were divided into 2 cohorts; those who developed sepsis and a control group. Sepsis was defined by combination of SIRS and clinical/radiological suspicion of infection. NLR was calculated by dividing the percentage of neutrophils by percentage of lymphocytes in peripheral blood.

Results: 127 out of 314 patients (40.5%) having at least one episode of sepsis post-operatively were included in the septic cohort and were compared to the 187 (59.5%) patients in the control group. Demographic and baseline characteristics including NLR (13.74 ± 0.99 vs 12.65 ± 0.57, p=0.294) were comparable preoperatively. The NLR of the septic cohort was significantly higher than the control cohort (15.01 ± 1.67 vs 9.98 ± 0.63, p=0.001) 3 days prior to sepsis and remained significantly higher till the day of sepsis. The area under the cover was maximum for NLR 1 day prior to the development of sepsis (r=0.707) with a sensitivity, specificity, positive predictive value and negative predictive value of 62.4%, 62.2%, 51.4% and 72.0% respectively at a cutoff of 8.5.

Conclusion: NLR is a useful tool in diagnosing and pre-empting development of sepsis in LDLT.
INTRODUCTION

Innovation in surgical techniques and improved peri-transplant care has improved outcomes post liver transplantation. 1 Sepsis, however remains the most common cause of post-transplant morbidity and mortality in patients undergoing LT. 2 Traditionally utilized markers of sepsis and bacteremia such as total leukocyte count, neutrophilia and lymphocytopenia has been explored at length in existing literature are limited by their low specificity and the ability to provide limited additional clinical information.3 Newer markers such as IL-6, sRAGE have been limited in their utility and adoption in clinical practice.4,5

The neutrophil-lymphocyte ratio (NLR) is an easily calculable inflammatory biomarker calculated by dividing the percentage of neutrophils by the percentage of lymphocytes in peripheral blood NLR originally found utility as a surrogate for the degree of systemic inflammation predicting development of sepsis in ICU patients. 6 NLR has also been described as an independent predictor of development of decompensation in cirrhotics with a higher mortality in patients listed for transplant. 7,8 Its role in predicting and diagnosing sepsis in recipients of solid organ transplants has not been described in literature. The aim of this study was to utilize NLR to diagnose and predict onset of clinical sepsis in patients undergoing living donor liver transplant (LDLT).

MATERIALS AND METHODS

This is a single-center analysis of prospectively collected data of consecutive adult patients who underwent elective LDLT from January 2013 to June 2018.
The study was approved by the institute ethics committee (IEC/2017/48/MA08) and was carried out in accordance with the Declaration of Helsinki. Patients were cleared by an independent legal authorization committee and an informed written consent was taken prior to LDLT. A standard protocol-based pre-operative, intra-operative and post-operative approach which has been previously published was followed for all the patients who underwent LDLT. 9,10

Sepsis was defined as per center for disease control guidelines as a combination of systemic inflammatory response syndrome and suspicion of infection (clinical or radiological suspicion of infection), with or without the presence of culture positivity 11. Septic shock was defined as requirement of vasopressor support to maintain a mean arterial pressure of 65 mm Hg. Patients demonstrating only culture positivity on ascitic fluid or vascular access device tips but no clinical evidence of sepsis were deemed to not fulfil the definition of sepsis.

Transplant recipients underwent blood investigations at baseline (prior to transplantation) and daily afterward till their discharge. The neutrophil-lymphocyte ratio was calculated by dividing the absolute number of neutrophils by the absolute number of lymphocytes in peripheral blood. Patients underwent routine microbiological screening (paired blood cultures, urine culture, ascitic fluid culture, nasopharyngeal swab or sputum culture) prior to operation, on post-operative day 3 and whenever clinical suspicion of sepsis arose.

Patients received routine peri-operative and post-operative antibiotic prophylaxis consisting of intravenous piperacillin-tazobactam (4.5 gram/q8hr), intravenous metronidazole (500 mg/q8h), intravenous teicoplanin (200mg/daily) for 72 hours. Routine antifungal prophylaxis was administered in the form of injectable Fluconazole 200 mg for 72 hours, followed by oral
Fluconazole for a cumulative period of 1 month. Pneumocystis pneumonia prophylaxis consisted of sulfamethoxazole/trimethoprim (480 mg/day by mouth). Routine CMV prophylaxis was not initiated unless there was the presence of CMV DNA detected in the pre-transplant period or presence of donor positive and recipient negative CMV status.

Post-transplant immunosuppression protocol which has been previously published was followed consisting of methylprednisolone 100mg administered in the anhepatic phase followed by 5 days taper(7). Maintenance immunosuppression consisted of tacrolimus + mycophenolate mofetil + prednisolone. Steroids were tapered in the majority of patients by the end of 3 months. Mycophenolate mofetil was started after platelet count increased to more than 50×10⁹/l post-transplant. The use of tacrolimus in the postoperative period was guided by serial liver and kidney function tests, rather than target drug levels. Usual target levels were 5–7 ng/ml in the first week. Patients were discharged from the hospital once they were ambulatory, had stable graft function, when all drains were removed (ascitic output < 200 mL), and were on stable immunosuppression.

**STATISTICAL ANALYSIS:**

Continuous variables were expressed as medians and interquartile range (IQR). Continuous variables were compared with the Student’s t-test and Mann-Whitney test as appropriate. Differences between proportions derived from categorical data were compared with chi-square or Fisher’s exact test. For all tests, a p-value of less than 0.05 was considered significant. A normally distributed continuous variable was compared using the student t-test or Mann-Whitney test for non-parametric variables. Categorical variables were compared by Fisher exact test or Pearson’s Chi-square test. Repeated measure (Generalized Estimating Estimate) was used to see the changes
over time. AUC (area under curve) was calculated by using ROC (receiver operating characteristic) curve method. Analyses performed on SPSS Statistics 22 for Windows (IBM).

RESULTS

From a total of 435 patients, pediatric recipients (n=63), acute liver failure (n=48) and ABO incompatible liver transplants (n=7) were excluded. Patients with incomplete hospital records (n=5) or post operative mortality within 72 hours (n=4) were excluded (Figure 1). The data from the remaining 314 patients was analyzed.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The preoperative, intraoperative and postoperative details of the patient population are described in Table 1. The median age of the patient population was 46.9 (IQR = 41 – 53) years with the majority being male (n=279, 88.8%). Most of the patients were transplanted for decompensated cirrhosis (n= 274, 87.1%), though a significant proportion were suffering from acute on chronic liver failure (n=40, 12.9%). The most common etiology of cirrhosis was related to ethanol (n=135, 42.9%) followed by cryptogenic (n=54, 17.2%). The median MELD Na at the time of transplantation was 23.8 (IQR = 20-27). The most common type of graft utilized was a right lobe graft without the MHV (n=257, 81.8%) with a median GRWR of 0.92 (IQR 0.81-1.1).

SEPSIS

A total of 127 patients (40.4%) experienced at least one episode of sepsis during their post operative course. Sixty-nine of these 127 patients (46%) developed septic shock requiring
inotropic support. The median day of development of sepsis was post operative day 7 (IQR = 4-11 days). In case there was more than 1 episode of sepsis in the same patient, only the first episode was considered for analysis. The median hospital stay was 23.13 days (IQR = 19–30 days) with a median follow up of 24.2 months (IQR: 7 – 37 months).

A total of 183 (57.3%) of the 314 patients demonstrated microbial culture positivity in at least one of their cultures during the post-operative period. The most common source of culture positivity was from ascitic fluid (118/314, 37.5%) and the bloodstream (76/314, 24.2%) (Figure 2).

We could not identify any statistically significant preoperative predictors of sepsis in our population (Table 2). A definite correlation was found between mortality and the development of sepsis (HR= 4.26, 95% CI 1-16.6, p < 0.001) Patients who developed sepsis had significantly poorer short term with a 90-day mortality of 22.8% (22/127). The 1 and 3 year survival for the septic cohort were 85.6% and 85.6 % which was significantly inferior to 97.2% and 95.7% of the non-septic cohort (p=0.001)

NLR

The NLR between the patients is comparable at baseline between the control and the septic cohort (12.65 ± 0.57 vs 13.84 ± 0.99, p=0.294) (Table 3). After an initial increase in NLR in the immediate perioperative period, the NLR in both groups can be seen to show a sharp fall remaining comparable till postoperative day 3. The NLR continues to fall in the control population, whereas in the septic group it starts rising again, peaking on the median day of development of sepsis which is on post operative day 7. (Figure 3)
The area under the cover was maximum for NLR 1 day prior to development of sepsis ($r=0.71$) with a sensitivity of 62.4% and specificity of 62.2% at a cutoff of 8.5. An NLR of less than 8.5 had a negative predictive value of 72.0% and a positive predictive value of 51.4% in predicting sepsis. Even 3 days prior to development of sepsis, NLR could predict development of sepsis with a moderate sensitivity of 67.3% and specificity of 51.2% and an AUC of 0.640 (Figure 4). NLR proved to be more robust at predicting sepsis as compared to traditional markers of sepsis (Figure 5).

**DISCUSSION**

The prompt and reliable diagnosis of sepsis remains a clinical challenge, none more so than in the cohort of immunosuppressed recipients of solid organ transplant. $^{12}$ Numerous attempts have been made to supplement traditionally used biochemical tests such as total leukocyte count (TLC), C-reactive protein (CRP) and procalcitonin with new and innovative biomarkers such as IL-1b, TNF $\alpha$ and sRAGE. $^{13}$ A combination of high cost, long turnaround time, poor availability and a lack of standardization between laboratories mean most liver transplant programs still utilize standard biochemistry for the crucial day to day management decisions of transplant recipients. The simple and easy to calculate NLR serves to utilize the differential response of neutrophils and lymphocytes to microbial infection to increase the diagnostic accuracy of traditionally utilized tests like TLC and bandemia. $^{14}$ To the best of our knowledge this is the first study to demonstrate a significant correlation of post-operative NLR with development of sepsis in patients undergoing LDLT.
The incidence of sepsis in our study is comparable to similar studies published in literature. The high incidence can be attributed to a combination of factors including, the relatively high MELD Na of most patients with a significant proportion of recipients suffering from acute on chronic liver failure at the time of transplant.

The NLR of both the groups was comparable at baseline and showed an initial postoperative peak. A similar rise is seen in the literature for other biomarkers such as procalcitonin after transplantation and can be attributed to a surgical stress response. While there was a gradual decrease in the NLR of the non septic cohort, the NLR of patients who developed sepsis continues to remain elevated. Three days prior to development of sepsis, a significant difference in the NLR can be noted between the two groups which continues to remain high till the date of onset of clinical sepsis.

Raised NLR has been consistently associated with outcomes in critically ill patients, reflecting an underlying immune dysregulation. A recently published meta-analysis of 14 studies demonstrated a significantly higher NLR in non-survivors than in survivors of sepsis. Higher NLR ratios have been correlated with an increase in infectious complications and infection related mortality in patients who underwent liver transplantation for ACLF. On the contrary, NLR values that decrease despite the surgical stress in the immediate perioperative period of a transplant has been correlated with poor graft survival. NLR has also been noted to be a better indicator of bacteremia as compared to conventional markers such as TLC, CRP and neutrophil count in critically ill patients, though it has been shown to be inferior to procalcitonin. The ROC of
NLR in our study was 0.71 which is similar to that quoted in literature and compares favorably with known markers of sepsis such as thrombocytopenia. We believe ours is the first study to evaluate the importance of NLR in the context of infectious complications after living donor liver transplant.

An important finding of our study is that NLR was significantly elevated in septic patients up to 3 days prior to clinical onset. This is an exciting and novel finding potentially allowing for an early and pre-emptive diagnosis of sepsis. Acute phase reactants currently in use such as erythrocyte sedimentation rate, CRP and procalcitonin are known to rise 4-12 hours after onset of sepsis and peak within 24-48 hours. Septic episodes in solid organ transplant recipients are characterized by a rapid and overwhelming course. Early identification of sepsis in these patients is made more challenging because of similar clinical presentations of complications such as acute cellular rejection, bilio-vascular complications and transfusion reactions.

The mean NLR in a healthy population was determined to be 1.65 across all ages. Trying to determine a cutoff for infectious pathology has proven to be more challenging. There is significant heterogeneity in literature regarding the ideal cut-off for NLR, because of different patient cohorts included and different cut-offs utilized to determine significance. In our study utilizing a cutoff of 8.5 NLR could predict sepsis in our study with a sensitivity of 62.4% and specificity of 62.2%. Another takeaway from the study is also analysis of the temporal trend of NLR. A persistently elevated or gradually rising NLR may be a predictor of ongoing/developing sepsis.
The major limitations of the current study is that inflammatory ratios by definition are surrogate markers for the severity of inflammation in the body. Many factors including surgical stress, liver regeneration after LDLT, ongoing rejection and sepsis contribute to the inflammatory state prevalent in these patients limiting the utility of NLR. Defining an absolute cutoff for NLR is also difficult because of the multifactorial nature of the post operative phase. Measurement of procalcitonin and CRP would have perhaps strengthened the correlation of NLR to sepsis in this study but are not routinely performed at our center.

In conclusion, the rise in NLR preceded the onset of clinical sepsis by 3 days and could prove to be a simple, easily calculable and readily applicable test that may allow early identification of sepsis in this cohort of patients. Like its peers CRP and procalcitonin, while NLR may not be sufficient for diagnosis of sepsis, it can still be a valuable adjunct in its timely detection.

DECLARATIONS:

No external funding was taken for this study

No conflict of interest

No patient interventions were performed. The study was cleared from the ethical committee of the hospital

Consent to participate – not relevant
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DECLARATIONS/STATEMENTS.

1. The raw data used for the use of publication of this manuscript is available in excel format.

2. No animal research was done.

3. This was a retrospective analysis of prospectively collected data with no intervention in the patient population. A consent to utilize patient clinical data for the use of research is taken for all patients undergoing liver transplantation. The same was utilized for the purpose of this study.

4. Consent to publish – this publication was part of a study that was cleared by the university/hospital ethical committee to analyze laboratory parameters and post operative outcomes in living donor liver transplants (Ethical clearance attached).

5. Plant reproducibility – not applicable.

6. Author Contribution

   Dr. Viniyendra Pamecha – Study conceptualization and design, Collected data, Contributed data, Wrote the paper, performed the analysis

   Dr. Shashwat Sarin – study conceptualization and design, Collected data, performed the analysis, wrote the paper

   Dr. Piyush Sinha – Contributed data

   Dr. Nilesh Patil – Contributed data

   Dr. Nihar – Contributed data

7. There is no conflict of interest from any of the authors.

8. No external funding was taken for this study.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients</th>
<th>No Sepsis</th>
<th>Sepsis</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 314)</td>
<td>(N=187)</td>
<td>(N=127)</td>
<td></td>
</tr>
<tr>
<td>Age (yrs.)</td>
<td>46.93 (41 – 53 yrs)</td>
<td>47.575</td>
<td>45.85</td>
<td>0.114</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>279/35 (88.8%)</td>
<td>166/21</td>
<td>113/14</td>
<td>0.995</td>
</tr>
<tr>
<td>MELD Na</td>
<td>23.7 (20-27)</td>
<td>23.37</td>
<td>24.45</td>
<td>0.101</td>
</tr>
<tr>
<td>CLD/ACLF</td>
<td>274 (87.1%)/ 40 (12.9%)</td>
<td>165/22</td>
<td>109/18</td>
<td>0.530</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>135 (42.9%)</td>
<td>77</td>
<td>55</td>
<td>0.417</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>54 (17.2%)</td>
<td>29</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>32 (10.2%)</td>
<td>23</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>23 (7.3%)</td>
<td>16</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>NASH</td>
<td>38 (12.2%)</td>
<td>24</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>35 (11.2%)</td>
<td>18</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Type of Graft</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Lobe w/o MHV</td>
<td>257 (81.8%)</td>
<td>160</td>
<td>97</td>
<td>0.163</td>
</tr>
<tr>
<td>Right Lobe + partial MHV</td>
<td>10 (3.2%)</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Left Lobe</td>
<td>45 (14.3 %)</td>
<td>20</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Right Posterior</td>
<td>2 (0.7%)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>GRWR</td>
<td>1.01 (0.81 – 1.17)</td>
<td>1.02</td>
<td>1.00</td>
<td>0.142</td>
</tr>
<tr>
<td>Cold Ischemia Time (min)</td>
<td>653.44 (570 - 756)</td>
<td>663.14</td>
<td>639.1</td>
<td>0.443</td>
</tr>
<tr>
<td>Warm Ischemia Time (min)</td>
<td>32.03 (22 - 39)</td>
<td>32.7</td>
<td>31.3</td>
<td>0.341</td>
</tr>
<tr>
<td>Blood Loss (ml)</td>
<td>3329 ml (1500 – 3950 ml)</td>
<td>3328.57</td>
<td>3397.7</td>
<td>0.855</td>
</tr>
<tr>
<td></td>
<td>23.13 (19 d – 30 d)</td>
<td>24.16</td>
<td>34.16</td>
<td>0.81</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------</td>
<td>-------</td>
<td>-------</td>
<td>------</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Follow Up (months)</td>
<td>24.2 (7-37) months</td>
<td>27.22</td>
<td>18.76</td>
<td>0.56</td>
</tr>
<tr>
<td>Acute Cellular Rejection</td>
<td>45/314 (14.3%)</td>
<td>27</td>
<td>18</td>
<td>0.681</td>
</tr>
<tr>
<td>Mortality</td>
<td>35/314 (11.14%)</td>
<td>13</td>
<td>22</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 1: Pre-operative, intra-operative and post operative predictors of development of sepsis.

Variables are mentioned as n(%) or median (interquartile range). MELD Na- Model for end stage liver disease Sodium, ACLF – acute on chronic liver failure, CLD – chronic liver disease, GRWR – Graft recipient weight ratio.
Table 2: Comparison of neutrophil lymphocyte ratio between control and sepsis groups at different time points

<table>
<thead>
<tr>
<th>Date</th>
<th>NLR – Control</th>
<th>NLR - Sepsis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>12.65 ± 0.57</td>
<td>13.74 ± 0.99</td>
<td>0.294</td>
</tr>
<tr>
<td>3 days prior to sepsis</td>
<td>9.98 ± 0.63</td>
<td>15.01 ± 1.67</td>
<td>0.002</td>
</tr>
<tr>
<td>2 days prior to sepsis</td>
<td>9.4 ± 0.59</td>
<td>13.45 ± 1.38</td>
<td>0.004</td>
</tr>
<tr>
<td>1 day prior to sepsis</td>
<td>8.51 ± 0.5</td>
<td>14.54 ± 1.32</td>
<td>0.001</td>
</tr>
<tr>
<td>Day of clinical onset of sepsis</td>
<td>8.10 ± 0.45</td>
<td>15.02 ± 1.65</td>
<td>0.001</td>
</tr>
</tbody>
</table>
### Area Under the Curve

<table>
<thead>
<tr>
<th>Variable</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLR</td>
<td>.705</td>
</tr>
<tr>
<td>Neutrophil Count</td>
<td>.605</td>
</tr>
<tr>
<td>Lymphocyte Count</td>
<td>.456</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>.495</td>
</tr>
<tr>
<td>TLC</td>
<td>.586</td>
</tr>
</tbody>
</table>

Table 3. Area under the curve for NLR and traditional markers of sepsis one day prior to onset of sepsis.
Total Liver Transplants in study period (n=435)

- Exclusions
  - Pediatric - including Acute liver failure (n = 63)
  - Adult acute liver failure (n = 42)
  - ABO Incompatible (n = 7)

Eligible patients (n=323)

- Exclusions
  - Incomplete Data (n = 5)
  - Early Mortality (n = 4)

Number Included in study (n=314)

- No Sepsis (n = 187)
- Sepsis (n = 127)
Figure 2: Source of microbial culture positivity.
Note: Some patients may have culture positivity from multiple sources
Author Contribution

Dr. Viniyendra Pamecha – Study conceptualization and design, Collected data, Contributed data, Wrote the paper, performed the analysis

Dr. Shashwat Sarin – study conceptualization and design, Collected data, performed the analysis, wrote the paper

Dr. Piyush Sinha – Contributed data

Dr. Nilesh Patil – Contributed data

Dr. Nihar – Contributed data