Serum Lipid Alterations in Early Rheumatoid Arthritis Patients on Disease Modifying Anti Rheumatoid Therapy

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Abstract Dyslipidaemia is a major CVD risk factor in the general population. Current evidence suggests that lipid metabolism is altered in RA due to inflammation, and that use of anti-inflammatory therapy may reverse some of these changes. The objective of our study is to compare the effect of treatment with DMARD on lipid fractions after 6 months of therapy. Forty patients who met the American College of Rheumatology, ACR/EULAR criteria for rheumatoid arthritis, with disease duration of less than 1 year and no prior treatment were included in the study. Thirty healthy volunteers were included as controls. The mean DAS-28 at disease onset was 5.15 ± 1.3 . Early Rheumatoid Arthritis (ERA) patients exhibited higher serum levels of total cholesterol (TC) and lowdensity lipoprotein cholesterol (LDL-C) and lower serum high-density lipoprotein cholesterol (HDL-C) levels compared to controls. As a consequence, the atherogenic index of plasma [$\log (TG/HDL-C)$], the atherogenic indices: TC/HDL-C as well as LDLC/HDL-C was significantly higher in ERA patients compared to controls. After 6 months of treatment, there was significant reduction of the DAS 28, HDL-C and Apo A-I improved and Lp(a) decreased significantly. All lipid ratios improved, a phenomenon primarily due to the increase in serum HDL-C levels. These changes were inversely correlated with CRP and ESR. In conclusion, ERA patients are characterized by an atherogenic lipid profile, which improves with DMARD therapy.

Keywords Apolipoproteins · Atherosclerosis · Small dense LDL-C · Log (TG/HDL-C) · Cardiovascular risk · Lp(a) · Atherogenic indices

Introduction

Rheumatoid arthritis (RA) is the most common form of chronic inflammatory arthritis of unknown etiology marked by symmetric, peripheral polyarthritis which often results in joint damage, physical disability and premature mortality [1]. Prevalence of RA in the general population worldwide is estimated to be between 0.5 and 1 % [2]. Although RA can occur at any age, its incidence increases with age and may vary depending upon the type of classification criteria used and demographics of the population studied.

RA is known to reduce the lifespan of patients as they suffer a double risk of heart disease [3], independent of other risk factors such as diabetes, alcohol abuse and elevated cholesterol, blood pressure and body mass index. The mechanism by which RA causes this increased risk remains unknown while high levels of systemic inflammation have been identified as an independent risk factor for plaque development [4]. Estimated standardized mortality ratios (SMR) associated with RA range from 1.3 to 3.0 and this increased mortality is largely attributed to cardiovascular disease (CVD) particularly coronary atherosclerosis.

Dyslipidaemia appears to manifest in RA patients in both early [5] and advanced disease [6]. Atherogenic lipoprotein phenotype, characterized by decreased high density lipoprotein-cholesterol (HDL-C), moderately raised triglycerides (TG) and increased levels of small dense LDL(sdLDL) is linked to increased cardiovascular risk, much more than low density lipoprotein-cholesterol

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(LDL-C) levels alone. In fact, not only the quantity of LDL-C, but the composition exerts a direct influence on cardiovascular risk and the predominance of small dense LDL (sdLDL) has been accepted as an emerging cardiovascular risk factor by the National Cholesterol Education Program Adult Treatment Panel III [7].

The primary site of inflammation in RA is the synovial tissue, from which cytokines are released into the systemic circulation. Thus, measurable levels of tumor necrosis factor- α (TNF- α), IL-1, and IL-6 are commonly present at several-fold higher levels in plasma than noted during the low-grade inflammation [8]. These circulating cytokines are in a position to alter the functioning of adipose tissue, skeletal muscle, liver, and vascular endothelium and generate a spectrum of proatherogenic changes that includes insulin resistance, a characteristic dyslipidemia, pro-thrombotic effects, pro-oxidative stress and endothelial dysfunction.

Assessment of plasma Apolipoprotein A-I (Apo A-I) and Apolipoprotein B (Apo B) allow an assessment of the total number of anti-atherogenic and pro-atherogenic particles, respectively. Adequate stratification of CVD risk has special relevance in RA patients. So we proposed to study the dyslipidemia in early RA (ERA) and the effect of treatment on lipid fractions and of atherogenic ratios.

Materials and Methods

We included in the present study 40 drug naïve patients with early RA who attended the department of Rheumatology, Nizam's Institute of Medical Sciences, Hyderabad between April 2013 and December 2013. Patients who fulfill ACR/EULAR 2010 Rheumatoid Arthritis criteria and with duration of disease of more than 6 weeks and less than 1 year without prior use of Disease modifying anti rheumatoid drugs (DMARD) and systemic steroids were included in the study. As controls, thirty age and sex matched healthy subjects were recruited. As per the protocol all patients received combination of corticosteroids (5–7.5 mg), hydrochloroquine (200 mg) and methotrexate (15–20 mg per week). Monitoring of side effects done as per standard protocol.

Exclusion Criteria

Smokers and patients suffering from conditions that affect lipid levels such as Diabetes Mellitus, Hypothyroidism, Liver and Kidney Disease, Cushing disease, obesity (BMI > 30), family history of dyslipidemia and drugs such as lipid lowering drugs, beta blockers, oral contraceptive

pills, estrogens, progesterone, vitamin E and other drugs were excluded from the study.

Out of 40 cases, 27 patients returned for follow up after 6 months of treatment and thirteen patients were lost to follow up. Apolipoproteins and sdLDL were analyzed in these cases, pre and post treatment. The study was approved by the hospital Institutional Ethical Committee(4th ESGS—NO.42/13). All patients gave written informed consent for the study.

Laboratory Assessment

Total cholesterol (TC) was estimated by CHOD-PAP (Enzymatic colorimetric method), HDL-C by HDL-C plus 3rd generation, no pretreatment, LDL-C by 2nd generation -LDL-Cholesterol, no pretreatment by Homogeneous enzymatic colorimetric assay, TG by enzymatic colorimetric test, Lipoprotein (a) by Tina quant lipoprotein a particle enhanced immunoturbidometric assay were used (Cobas C 501, Roche Diagnostics, North America). Very low density lipoprotein -cholesterol (VLDL-C) was calculated using Friedewald's equation. Apo A-I and Apo B measured by Immunoturbidometric principle (Randox Laboratories Ltd., Co. Antrim, United Kingdom). Small dense LDL was done by manual precipitation method as described by Hirano et al. [9].

Lipid Ratios

1. Atherogenic index of plasma(AIP): Log (TG/HDL-C); TG and HDL-C estimated by above mentioned assay, were converted into mmol/L then divided and log transformed.
2. TC/HDL-C
3. LDL-C/HDL-C and
4. Apo B/Apo A-I were also calculated.

Statistical Analysis

The statistical analysis was done by Graphpad prism Version 6. The mean and standard deviation for the variables was calculated. In the baseline cases and controls, normally distributed variables were analyzed by independent t- test. Non-normally distributed variables were analyzed by Mann-Whitney U test. Correlation between variables was done by Spearman Rank correlation analysis. In the follow up group normally distributed variables were analyzed by paired t test. Non-normally distributed variables were analyzed by Wilcoxon signed rank test. A *p* value of <0.05 was taken as statistically significant.

Table 1 Demographic variables in cases (n = 40)

Variable	Mean	± SD	95 % CI
AGE (years)	35.93	8.91	33.07–38.78
ACR score	8.15	1.49	7.67–8.63
BMI (kg/m ²)	25.21	4.34	23.82–26.6
DAS 28	5.15	1.3	4.73–5.56
Hemoglobin (g/dL)	11.66	1.66	11.1–12.23
TLC (/mm ³)	9324.17	3458.59	8153.95–10,494.39
Platelets (lakhs/mm ³)	3.06	0.94	2.72–3.4
ESR (mm/hr.)	42.59	23.11	34.89–50.3
SGOT (U/L)	25.54	12.22	21.47–29.61
SGPT (U/L)	29.84	25.28	21.41–38.27
Serum Creatinine (mg/dL)	0.82	0.19	0.75–0.88

Results

A total of 70 subjects (40 cases and 30 controls) were included in this study. Among the 40 cases, 30 were females and 10 males. In the control group of 30 healthy subjects, there were 23 females and 7 males. The mean ± SD of age in the patients and controls subjects are 36 ± 8.91 and 35 ± 9.8 years, respectively and the difference was not statistically significant. The percentage positivity of IgMRF in cases is 80 % and the percentage positivity of Anti Citrullinated protein antibody in cases is 87 % (Table 1).

All the lipid parameters and lipid ratios were compared at baseline between cases and controls.

Table 2 shows comparison of lipid parameters in cases and controls. TC, LDL-C and Lp(a) are significantly higher in cases than controls. TG and VLDL-C were similar in cases and controls. Our results indicate that compared to

Table 3 Comparison of Atherogenic indices in cases and controls

Parameter	Cases	Controls	<i>p</i> value
log (TG/HDL-C)	0.13 ± 0.28	0.008 ± 0.135	0.0276 ^{a*}
TC/HDL-C	4.54 ± 1.52	3.46 ± 0.57	0.0004 ^{a*}
LDL-C/HDL-C	2.8 ± 1.23	1.99 ± 0.49	0.0012 ^{a*}
Apo B/Apo A-I	0.62 (0.45–0.85) [#]	0.60 (0.54–0.86) [#]	0.4972 ^b

Normally distributed data is expressed as Mean ± SD

[#] Non-normally distributed data expressed as Median (25th–75th percentile)

p value was calculated between cases and controls by: a = independent group t test, b = Mann–Whitney U test, * *p* < 0.05-statistical significance

the general population patients with early active RA before therapy have an atherogenic lipid profile characterized by significantly higher TC-15 %, LDL-C-19 %, Lp(a)-39 % at base line compared to controls. The HDL-C was lower by 11 % and the TG by 4 %.

Among the lipid ratios, the atherogenic index of plasma (AIP) is higher in RA patients and statistically significant. The atherogenic ratios: TC/HDL-C (>3.5) and also LDL-C/HDL-C are significantly higher in cases than in controls. The Apo B/Apo A-I ratio (>0.5) indicates higher risk (Table 3).

Post Treatment Effect on Lipid Parameters

After six months of treatment, 27 cases came for follow up of which 19 were females.

The DAS 28 showed significant improvement after treatment (*p* < 0.0001) (Table 4). A significant improvement was noted in the HDL-C fraction (34 %) among the

Table 2 Comparison of Lipid parameters among cases and controls

Parameter	Cases	Controls	<i>p</i> value
TC (mg/dL) (n = 40)	171.5 ± 37.33	146.3 ± 17.55	0.0011 ^{a*}
HDL-C (mg/dL) (n = 40)	37.5 (30.25–48.75) [#]	42 (37–48.25) [#]	0.1033 ^b
LDL-C (mg/dL) (n = 40)	103.6 ± 31.73	83.77 ± 15.99	0.0025 ^{a*}
VLDL-C (mg/dL) (n = 40)	23 (16–39)	21.5 (15–24.25)	0.1375 ^b
TG (mg/dL) (n = 40)	115 (79.25–193.8) [#]	110.5 (75–121.5) [#]	0.1317 ^b
Apo A-I (mg/dL) (n = 27)	107 (86–137) [#]	134 (115.3–136) [#]	0.0059 ^{b*}
Apo B (mg/dL) (n = 27)	65.89 ± 15.88	85.87 ± 23.61	0.0005 ^{a*}
LP(a) (mg/dL) (n = 40)	37 (20.5–66.5) [#]	22.5 (19–27) [#]	0.0033 ^{b*}
sdLDL (mg/dL) (n = 27)	32.80 ± 10.81	30.03 ± 8.75	0.5688 ^a

Normally distributed data is expressed as Mean ± SD

[#] Non-normally distributed data expressed as Median (25th–75th percentile)

p value was calculated between cases and controls by: a = independent group t test, b = Mann–Whitney U test, * *p* < 0.05-statistical significance

Table 4 Comparison of Disease Activity Score and lipid fractions pre and post treatment (n = 27)

Parameter	Pre treatment	Post treatment	p value
DAS 28	5.7 (4.93–6.6) [#]	3.4 (3–4.88) [#]	<0.0001 ^{b*}
TC (mg/dL)	168 ± 37.25	166.6 ± 32.87	0.8144 ^a
HDL-C (mg/dL)	35 (31–45) [#]	47 (40–58) [#]	0.0003 ^{b*}
LDL-C (mg/dL)	99.52 ± 30.46	91.93 ± 28.04	0.1053 ^a
VLDL-C (mg/dL)	28.85 ± 15.61	25.44 ± 11.28	0.2701 ^a
TG (mg/dL)	145.6 ± 76.24	127.2 ± 56.64	0.2175 ^a
LP(a) (mg/dL)	36 (15–70) [#]	30 (12–51) [#]	<0.0001 ^{b*}
sdLDL (mg/dL)	31.93 ± 15.56	27.99 ± 16	0.3713 ^a
Apo A-I (mg/dL)	107.5 ± 27.54	123 ± 22.41	0.0208 ^a
Apo B (mg/dL)	65.89 ± 15.88	60.26 ± 19.11	0.1681 ^a

Normally distributed data is expressed as Mean ± SD

[#] Non-normally distributed data expressed as Median (25th–75th percentile)

p value was calculated between group by: a = paired t test, b = Wilcoxon signed rank test, * p < 0.05-statistical significance

lipid parameters. Apo A-I showed significant increase whereas Lp(a) (14.41 %) showed significant decrease while there was no significant change in the Apo B and sdLDL levels.

Significant changes are also noted in the atherogenic indices-TC/HDL-C, LDL-C/HDL-C, Apo B/Apo A-I and log TG/HDL-C (Table 5)

The association of lipid parameters with DAS28 is as follows.

As has been shown in Table 5, there was no significant correlation between DAS 28 and the different lipid fractions. Table 6 indicates a negative correlation of DAS 28 with HDL-C and positive correlation with triglyceride pre treatment.

Discussion

Cardiovascular risk in RA is enhanced through several factors such as hypertension, insulin resistance and obesity which occur more frequently in RA. Disease specific

Table 6 Spearman Correlation of baseline DAS 28 with lipid fractions in pre and post treatment (n = 27)

DAS 28 versus	Pre treatment		Post treatment	
	r value	p value	r value	p value
TC	−0.21	ns	−0.01	ns
HDL-C	−0.41	0.04	−0.04	ns
LDL-C	0.18	ns	0.01	ns
TG	0.45	0.02	0.11	ns
LP(a)	0.17	ns	−0.27	ns
Apo A-I	−0.32	ns	−0.04	ns
Apo B	0.2	ns	0.15	ns
SdLDL	0.1	ns	0.1	ns

ns non significant

factors such as systemic inflammation, activation of the coagulation pathway and hyper-homocysteinaemia also confer additional cardiovascular risk. High levels of systemic inflammation have been identified as an independent risk factor for plaque development and may exert this effect by increasing levels of oxidative stress, activation of coagulation and secondary dyslipidaemia. A genetic predisposition of RA patients to the development of atherosclerosis and myocardial infarction coupled with traditional risk factors increases their risk of CVD greatly [10].

Lipoprotein lipase is the principle catabolic enzyme for the TG-rich lipids and high TG levels reduce the HDL-C by virtue of the neutral lipid exchange and also promotes synthesis of small dense LDL particles [11]. A predominance of sdLDL particles is associated with a 3–5 times increased risk of coronary heart disease (the Quebec cardiovascular study) [12]. The inflammatory cytokines released into the circulation in RA patients, alters the lipid metabolism leading to increased free fatty acid (FFA) release from the adipose tissue, increased FFA and triglyceride synthesis in the liver and a reduced lipoprotein lipase activity with resultant dyslipidemia [13]. Inflammatory stress may also accelerate foam cell formation through mechanisms of enhanced LDL modification e.g.

Table 5 Comparison of AIP and lipid ratios Pre and Post treatment (n = 27)

Parameter	Pre treatment	Post treatment	p value
AIP-log (TG/HDL)	0.16 ± 0.29	0.04 ± 0.28	0.043 ^{a*}
TC/HDL-C	4.09 (3.35–5.97) [#]	3.43 (2.95–4.24) [#]	0.0022 ^{a*}
Apo B/Apo A-I	0.62 (0.45–0.85) [#]	0.48 (0.34–0.62) [#]	0.0272 ^{b*}
LDL-C/HDL-C	2.77 ± 1.20	2.11 ± 0.90	0.0008 ^{a*}

Normally distributed data is expressed as Mean ± SD

[#] Non-normally distributed data expressed as Median (25th–75th percentile)

p value was calculated between group by: a = paired t test, b = Wilcoxon signed rank test, * p < 0.05-statistical significance

oxidation, disruption of cholesterol mediated LDL receptor feedback, thus increasing the uptake of unmodified LDL and the CRP binding to native LDL particles may enhance uptake into macrophages by the CRP receptor CD32. Thus these factors combine to alter the composition of proatherogenic lipid particles and increase the risk of atherosclerosis and CVD in the predisposed RA individuals.

A preclinical follow-up study of lipid profiles by Van Halm Nielsen et al. [14] in 1078 blood bank donors, 79 of whom later developed RA, when compared with 1071 age and sex matched controls, displayed on an average, 4 % higher TC, 9 % lower HDL-C, 17 % higher TG and 6 % higher Apo B levels ($p < 0.05$), at least ten years before the onset of symptoms. This suggests that RA patients are genetically predisposed to the development of dyslipidaemias.

The apolipoproteins: both Apo A-I and Apo B are significantly lower in cases than in controls in our study. Elevated Apo B levels indicate an increased risk of cardiovascular disease, but in our study Apo B was 23 % decreased in cases when compared to controls. In a similar study, Magarò M et al. have also shown Apo A-I and Apo B to be significantly lower in RA patients. They have also shown reduced levels of albumin in these patients which perhaps indicate a reduced rate of synthesis of proteins by the liver reflected in the decreased levels of the apoproteins [15]. Study by Eva Hurt Camejo et al. [16] showed an Apo B decrease by 7 %, while Apo A-I, TC, TG, IDL and HDL were in the normal range in the RA patients and similar to those in the controls.

The high prevalence of abnormal blood lipids in RA patients is also supported by Indian studies. Study by Grover S et al. [17] demonstrated raised total cholesterol levels while Hadda et al. [18] showed that 38.5 % of the 96 patients in their study were dyslipidaemic, the commonest being low HDL-C in 34.3 % of the patients and a trend was observed towards the normalization of the lipids and a decrease in the disease activity in the follow up visits.

The ratio of TG/HDL-C is an easily obtainable atherogenic marker and is a powerful predictor of total mortality independent of important prognostic variables including age, race, smoking, hypertension, diabetes, and severity of coronary artery disease [19]. A high TG/HDL-C ratio correlates with LDL-C phenotype B (sdLDL), small HDL particles which are proatherogenic and insulin resistant. Atherogenic index of plasma (AIP) is calculated as $\log(\text{TG}/\text{HDL-C})$, with TG and HDL-C expressed in molar concentrations [20]. Interestingly, a significant increase in the atherogenic ratio index as indicated by $\log(\text{TG}/\text{HDL-C})$, $\text{TC}/\text{HDL-C}$ or $\text{LDL-C}/\text{HDL-C}$ observed in ERA patients, convincingly suggests that these patients are predisposed to a higher risk of atherosclerosis.

Effect of DMARDs on Lipid Parameters

Follow up patients were treated with DMARDs, mostly by a combination of methotrexate, hydrochloroquine, non-steroidal anti inflammatory drugs and corticosteroids. An important observation of our study is that after drug intervention, ERA patients exhibited significantly higher levels of HDL-C and Apo A-I serum level in parallel with the reduction in DAS 28 score. This increase in HDL-C levels also inversely correlated with the reduction in ESR values. This suggests that inflammation is an important determinant for the reduced HDL-C levels observed in ERA patients. Lipoprotein (a) was also significantly lower post treatment than at the baseline. Remaining parameters (TG, LDL-C and Apo B) in RA were much less susceptible to changes in inflammatory burden, and the use of anti-rheumatic drugs, including glucocorticoids within the 6 month duration. In a study by Soubrier Martin on 29 patients who received infliximab did not show changes in the lipid fractions and the atherogenic index indicating that the anti TNF therapy does not affect lipid metabolism [21].

Apo A-I was significantly higher in post treatment group as supported by Georgiadis et al. [22] who studied apolipoproteins levels in RA patients at baseline and after 12 months of treatment. They found that the baseline values of Apo A-I in RA patients were significantly lower than controls and showed a significant increase after treatment suggesting the beneficial influence of treatment on Apo A-I levels. Similarly, Park et al. [23] also reported a significant increase in Apo A-I levels in RA patients from their baseline values after 1 year of treatment. In another study by Peters et al. [24] on 80 RA patients on infliximab and corticosteroids, all the lipids were at baseline levels after 48 weeks of treatment while Apo A-I levels increased and remained elevated at 48 weeks. Glucocorticoids have been shown to induce Apo A-I promoter activity and gene expression through proximal promoter elements situated between nucleotides –235 and –144 [25]. Thus, the increase in Apo A-I levels found in the treatment group in our study may be explained as the effect of glucocorticoids administered to these patients.

There is no other study detailing the effects of non-biologic DMARD on lipid levels in early RA.

Lipoprotein(a) is recognized to be an independent CV risk factor in the general population and found to be increased in the Indian and Asian populations perhaps due to increased genetic expression. Post treatment Lp(a) showed significant decrease in our study, supported by similar findings by Hjeltne et al. [26] who examined the effect of methotrexate (MTX) with or without tumor necrosis factor alpha (TNF- α)-inhibitors on Lp(a). MTX or MTX combined with a TNF- α inhibitor appears to significantly reduce Lp(a) which suggests that Lp(a) might be

related to systemic inflammation, or that the examined drugs might reduce Lp(a) by other mechanisms.

The small dense LDL is particularly atherogenic because these are preferentially held by arterial wall and are also readily oxidised. They also carry the enzyme phospholipase A₂ which plays important role in atherosclerosis. Hypertriglyceridemia seems to be main predisposing factor for generation of sdLDL. When hepatic lipase activity increases it generates sdLDL by lipolysis [27]. We observed no significant difference in sdLDL levels post treatment.

The Apo B/Apo A1 ratio is another strong predictor of CV risk, with biologically normal values of <0.50, which is also the target in lipid lowering therapy. In the patients of ERA, pretreatment Apo ratio values of 0.62 (0.45–0.85) indicate mild CV risk which were improved to normal values of 0.48 (0.34–0.62) [28] post treatment. The atherogenic indices Log (TG/HDL-C), TC/HDL-C and LDL-C/HDL-C were also improved significantly. Thus lipid ratios appear to offer a more reliable method of identifying lipid abnormalities or the true extent of lipid-associated risk as also monitoring efficacy of therapy. Georgiadis et al. [22] reported significantly lower TC/HDL-C and LDL-C/HDL-C ratios in RA patients post treatment, compared to baseline values and suggested this is due to treatment induced increase in serum levels of HDL cholesterol.

Hydroxychloroquine, used in treatment of RA has been shown to increase HDL levels. HCQ may alter lipid profiles in RA patients either by a reduction in disease activity or by affecting lipid metabolism directly [29]. Corticosteroid usage also is found to be associated with an increase in HDL cholesterol levels [30]. Hence the increase in HDL cholesterol levels in RA patients undergoing treatment in the present study can be explained as an effect of treatment in these patients. Morris et al. [31] studied the effect of HCQ and reported that the use of HCQ in the RA cohort was independently associated with a significant decrease in LDL-C, TC, LDL-C/HDL-C, and TC/HDL-C.

In our study, we tried to exclude patients with classic risk factors for atherosclerosis and we found that ERA patients with high disease activity showed an adverse lipid profile before the commencement of therapy. After 6 months of treatment, a significant improvement in some lab parameters was noted. This improvement correlated with changes in the lipid profile, mainly the increase of HDL-C, Apo A-I and decrease Lp(a).

Limitations of Study

The sample size was small to allow for a generalization of the results. The long term effects of the treatment on lipids and disease activity can be deciphered only through further follow up.

Conclusion

The study demonstrates that in a cohort of early RA patients drawn from a tertiary referral centre in south India, the levels of TC, LDL-C and Lp(a) are higher and levels of HDL-C are lower while VLDL-C, TG, Apo-B, Apo A-I are not different from the controls. This study also demonstrates that after 6 months of treatment with DMARD, as the DAS declines in RA patients the HDL-C improves, Lp(a) decreases and Apo A-I increases. Hence ERA patients have higher atherogenic index of plasma with improvement after treatment. The management of dyslipidaemia in RA should be a part of the general cardiovascular risk management. Therefore, a good control of the disease activity should be the priority, given that both the quality of life and the long-term outcomes can be improved.

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Compliance with Ethical Standards

The study was approved by the hospital Institutional Ethical Committee (4th ESGS—NO.42/13).

Conflict of interest The authors: Dr. Sana Parveen, Dr. Rachel Jacob, Dr. Liza Rajasekhar, Dr. C. Srinivas, Dr. Iyyapu Krishna Mohan declare that we have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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