RESEARCH ARTICLE

ESTIMATION OF PRO-INFLAMMATORY MARKERS IN NIGHT SHIFT HEALTHCARE WORKERS AND IDENTIFY RISK FACTORS ASSOCIATED WITH IT

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ABSTRACT

Shift labor, with hours outside of the regular diurnal work cycle, is used to facilitate round-the-clock emergency healthcare services. This impacts the circadian rhythm, which can potentially activate the pro-inflammatory responses of the immune system. This study aimed to find out the levels of pro-inflammatory markers in night shift healthcare workers and find risk factors associated with their increase.

303 participants (doctors, nurses, technicians, health care aids) were recruited with 169 participants nightshift and 134 dayshift workers. Pro-inflammatory markers Highly Sensitive C-Reactive Protein (hsCRP) and Total Leukocyte Count (TLC)] were estimated. Factors were compared by t test, Wilcoxon Rank Sum test and Chi square test. Risk factors for hsCRP elevation were identified by logistic regression analysis.

Pro-inflammatory markers like hsCRP and TLC were significantly increased in night shift health workers in comparison to the day shift workers (hsCRP 0.30± 0.33 mg/dl vs 0.10± 0.09 mg/dl, TLC 8181.06± 1181.53 /cu mm vs 7473.80± 1018.81 /cu mm) respectively. Multivariate logistic regression analysis showed night shift work (OR 48.20 95% CI (4.99-465.61), age (OR 1.13 95% CI (1.01-1.26)) and BMI (OR 1.18 95% CI (1.06-1.32)) as independent predictors of elevated hsCRP after adjusting for other risk factors. Hence, night-shift work is an independent risk factor for a rise in pro-inflammatory markers. These findings might aid health care workers and policymakers strategize methods to tackle the challenges through providing support programs, counselling sessions to avoid ailments and deliver health services in a better way.

KEYWORDS

shift work, healthcare workers, inflammatory markers, hsCRP, TLC, BMI, lipid profile, cardio-metabolic diseases.

INTRODUCTION

Healthcare is one of the sectors that provides a continuous service round the clock, for the benefit of patients. Each healthcare professional is responsible for providing care through application of medical science, knowledge, skill and expertise. Hence healthy and psychologically balanced workplaces should be a priority for healthcare providers. Healthcare workers (HCWs) are bound to shift-work covering day and night in order to cover emergency needs. European observatory of working life survey (2016) has shown that 19% of HCWs (24% males and 14% women carried out night shift work in emergency unit [1].

Night shift work has physical, psychological and social effects on the life of an individual. It may cause severe long-term effects with regards to health, resulting in high economic cost for both the individual and society. Immediate problems associated with the shift work are sleep disturbances and fatigue [2]. An increasing number of studies shows that the effect of long-term night shift work on health includes cardiovascular diseases (such as angina pectoris and myocardial infarction (MI)), cerebrovascular diseases (such as stroke), metabolic syndrome, and mental illness (such as depression and sleep disorders), gastro-intestinal (GI) disorders, breast cancer and prostatic cancer [3]. In a study undertaken by Akersted and colleagues, white collar shift workers had a 2.6-fold higher mortality as compared to day-time workers [4]. An international agency for research on cancer categorized shift work, including night work, as a Group2A carcinogenic factor in humans [4]. Even the severity of these diseases is seen more in night shift workers compared to day shift staff. Non-traditional shift work, like rotating, early morning and night, usually stand out from typical work schedules and are often associated with extended episodes of wakefulness subjecting healthy individuals to inadequately adapt to the effects of shift work [5].

The health consequences of shift work are basically due to desynchronization between the circadian rhythm and environmental conditions. In addition, because individual biological rhythm re-entrains to a time shift at different rates, each time the work schedule rotates for a period of time after the time shift, the circadian system will be in a desynchronized state [6]. The major function of the circadian rhythm is internal cycling of physiological and metabolic events. Chronic disruption of circadian timing in shift work leads to higher risk of several pathologies. One potential common feature of the negative health consequences of circadian disruption may be dysregulation of the immune system. A comprehensive understanding of the effects of circadian disruption on immune function is lacking but evidence exists for bidirectional relationship between immune system and circadian timing. Both partial and total sleep deprivation/restriction increases the level of circulating pro-inflammatory cytokines [7].

Highly Sensitive C-Reactive Protein (hsCRP)) is a sensitive but non-specific inflammatory marker synthesized by the liver in response to stimulation by pro-inflammatory cytokines [8]. hsCRP and Total Leukocyte Count (TLC) are major risk factors as well as prognostic factors for cardiovascular diseases (CVD) and metabolic syndromes [9]. Nightshift work related circadian disruption has been associated with systemic inflammation [10]. Hence, these inflammatory markers can be used for early detection of long-term health side-effects of nightshift work and help their further prevention. Therefore, in this study we aim to find the levels of pro-inflammatory markers (hsCRP and TLC) in night-shift healthcare workers and find the risk factors associated with their increase.

MATERIAL AND METHODS

STUDY DESIGN, STUDY SETTING, STUDY POPULATION

This study was a hospital based cross-sectional observational study conducted in a tertiary healthcare setting of the Kalinga Institute of Medical Sciences, India. All the eligible health care workers (doctors, nurses, technicians and health care aids) in the age group 25-45 years were included for participation in the study and those with known inflammatory disorders, diabetes mellitus, hypertension and known CVD cases were excluded from the study.

Data collection and Investigations: A total 303 participants were recruited for the study with 169 participants from night shift and 134 participants of day shift HCWs who were taken as our control group. Frequency of night shift per month and the duration of exposure to night shift since worked (in years) were recorded. Histories regarding smoking, alcoholism and regular exercise was taken. Blood pressure was measured in a mentally and physically relaxed state with an average of a minimum three measurements of systolic and diastolic pressure (SBP, DBP) taken in mm of Hg. Weight and height of the participants were recorded and

Body Mass Index (BMI) was calculated. Waist circumference (WC) was measured in inches at the midpoint between lower border of rib cage and iliac crest.

5ml of fasting venous blood sample was collected under aseptic conditions. 1ml was kept in fluoride vials for plasma glucose estimation and 2ml in red topped vacutainers for lipid profile and hsCRP estimation. The rest of the amount was kept for TLC estimation in EDTA vials. After centrifuging and separation of serum, different parameters were analysed. Fasting blood sugar (FBS) was analysed by the hexokinase (HK) method. Serum cholesterol and triglycerides were done by enzymatic cholesterol oxidase peroxidase (CHOD-POD) and glycerophosphate oxidase – peroxidase (GPO-POD) methods respectively. Serum High Density Lipoprotein (HDL) was measured by the colorimetric non-HDL precipitation method and Low Density Lipoprotein (LDL) was calculated by the Friedewald's formula. hsCRP was estimated by particle enhanced turbidimetric assay ((hsCRP level ≤ 0.5 mg/dl was considered normal and > 0.5 mg/dl was considered elevated). All the parameters were analysed by a Cobas Integra 400 Plus analyzer (Roche diagnostics – Germany). The total leukocyte Count (TLC) was done in using a Beckmann Coulter LH 750 hematology analyser by impedance technology.

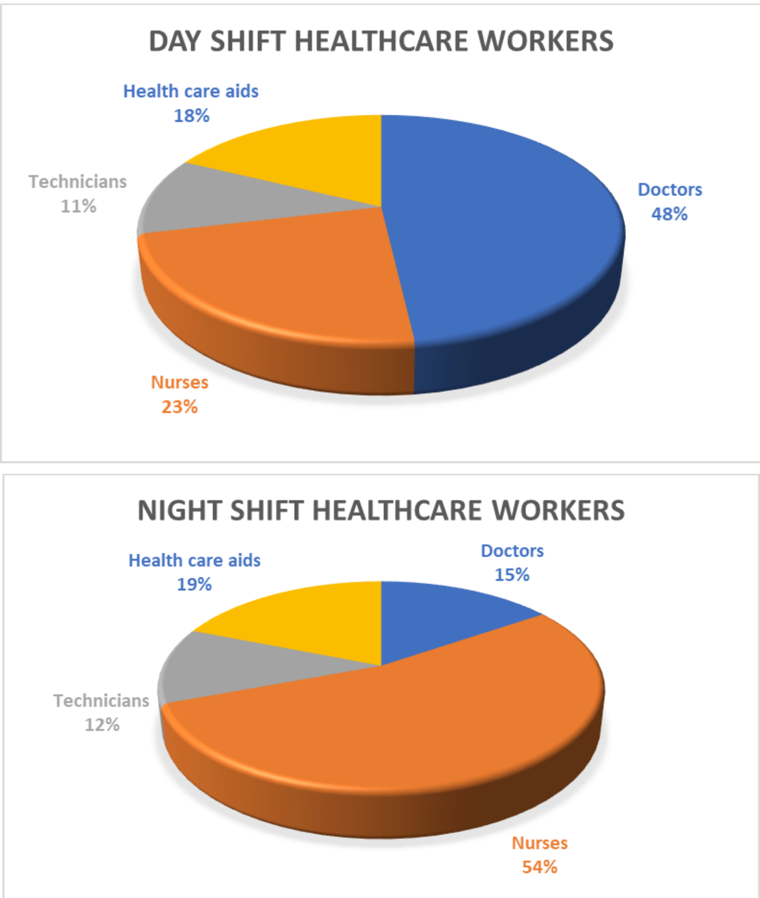
STATISTICAL ANALYSIS

All the continuous data obtained is described using mean, standard deviation and categorical data by their frequency (%). Factors were compared using t-test, Wilcoxon rank sum test and chi- square test. To identify risk factors for elevated hsCRP, logistic regression was used. The variable found significant under univariable regression analysis were the candidate variable for multivariable regression analysis after considering multi-collinearity. All the tests were interpreted at 5% level of significance. All the statistical analysis was done using StataCorp STATA software (version 15.1).

RESULTS

The cohort of HCWs recruited for the current study were from a renowned academic hospital in the eastern Indian state of Odisha. The job specifications of the HCW cohort recruited for this study has been depicted in Figure 1, which shows the majority of our study population were staff nurses (40.92%). In the night shift group, 53.84% were staff nurses whereas in day shift doctors were predominant at 51.49% of the group.

FIGURE 1: DISTRIBUTION OF HEALTHCARE PROFESSIONALS AMONG THE STUDY GROUP



The demographic and biochemical parameters of the HCW study group have been elucidated in Table 1. Individuals who worked in day shifts are on an average two years older than those who worked in night shifts, however, this difference was not statistically significant. BMI was similar in both the groups. Waist circumference was found to be significantly higher in night shift workers compared to their day shift peers (31.94± 6.37 inches and 30.79± 2.14 inches respectively) ($p<0.05$). SBP was significantly higher in night shift workers compared to the day shift workers. FBS, serum cholesterol, and LDL were significantly increased in night shift HCWs (82.59± 18.59 mg/dl, 173.22± 37.63 mg/dl, 106.15 ±28.22 mg/dl respectively) whereas there was no significant difference in serum TG between the two groups. Pro-inflammatory markers like hsCRP (0.30± 0.33 mg/dl vs 0.100± 0.09 mg/dl) and TLC (8181.06± 1181.53 /cu mm vs 7473.8± 1018.8 /cu mm) were significantly increased in night shift compared to day shift HCWs.

TABLE 1: DEMOGRAPHIC AND BIOCHEMICAL PARAMETERS OF THE STUDY GROUP

Sl.	Variables	Day Shift	Night shift	p-value
1	Age (in years)	29.5± 9.00	27.89± 6.57	0.07
2	BMI (Kg/m2)	23.11± 5.39	23.97± 5.35	0.17
3	Waist Circumference (in Inches)	30.79± 2.14	31.94± 6.37	<0.05*
4	SBP (mm of Hg)	114.38± 9.85	119.03± 12.94	<0.001*
5	DBP (mm of Hg)	74.04± 7.58	75.55± 7.92	0.09
6	FBS (mg/dl)	78.12± 8.55	82.59± 18.59	<0.05*
7	Cholesterol (mg/dl)	160.70± 27.29	173.22± 37.63	<0.001*
8	TG (mg/dl)	109.39± 38.77	118.84± 50.64	0.07
9	HDL (mg/dl)	40.17± 6.82	43.30± 9.40	<0.001*
10	LDL (mg/dl)	98.64 ±20.15	106.15 ±28.22	<0.05*
11	VLDL (mg/dl)	21.87± 7.75	23.76 ±10.12	0.07
12	hsCRP (mg/dl)	0.10± 0.09	0.30± 0.33	<0.001*
13	TLC (/cu.mm)	7473.80± 1018.81	8181.06± 1181.53	<0.001*

Next, we embarked upon performing the logistic regression analysis of hsCRP with various factors by both univariate and multivariate analysis (Table 2). Because of the multi-collinearity some of the variables (measured only in the night shift workers like for frequency of night shift, duration of night shift) and serum cholesterol, collinearity with HDL and LDL were not included in the multivariate analysis. Participants who were not previously diagnosed of diabetes mellitus or hypertension, but with elevated values were found on examination and those with history of smoking and alcoholism were excluded. While analysing for risk factors and predictors of hsCRP by regression analysis as these factors may themselves be responsible for increase in hsCRP [11]. After screening for the exclusion criteria, a total of 279 participants were then included for the analysis. Univariate regression analysis reveals hsCRP in the staff member doing night shift to be elevated 31-times in comparison to the daytime healthcare workers. However, after adjusting for other factors in the multivariate analysis, it reveals a 48-fold increase in hsCRP in night shift workers OR 48.20 95% CI (4.99-465.61).

Furthermore, age was also a significant factor for determination of hsCRP levels because with a year increase in age there was 0.08-fold elevation in hsCRP. Marital status was also a significant factor for elevated hsCRP because married HCWs had a 6-fold increase in hsCRP as compared to those unmarried. But after adjusting for other factors, it cannot be an independent predictor for elevated hsCRP. Our results suggest that higher BMI is also a reason for elevated hsCRP. SBP, HDL and LDL were found risk factors for elevated hsCRP but could not be predictors as they were not significant by multivariable analysis. Our multivariable analysis showed night shift, age and BMI as independent predictors of elevated hsCRP even after adjusting for other risk factors.

TABLE 2: LOGISTIC REGRESSION ANALYSIS FOR UNIVARIATE AND MULTIVARIATE VARIABLES

Factors		Univariate		Multivariate	
		OR (95% CI)	p value	OR (95% CI)	p value
Age		1.08(1.03-1.13)	<0.001*	1.13(1.015-1.26)	<0.05*
Gender	Male	1.00			
	Female	1.9 (0.86-4.32)	<0.001*		
Marital Status	Unmarried	1.00		1.00	
	Married	5.89(2.55-13.61)	<0.001*	1.36(0.35-5.27)	0.65
Shift work	Day	1.00		1.00	
	Night	31.26(4.20-232.22)	<0.001*	48.20(4.99-465.61)	<0.001*
Frequency of night shift work		1.22(1.11-1.34)	<0.001*		
Duration of night shift work (since years)		1.59(1.39-1.89)	<0.001*		
Exercise	No	1.00			
	Yes	0.135(0.08-0.2)	0.68		
Waist Circumference		1.04(0.98-1.09)	0.127		
BMI		1.19(1.11-1.28)	<0.001*	1.18(1.06-1.32)	<0.001*
SBP		1.07(1.04-1.11)	<0.001*	1.03(0.99-1.07)	0.104
DBP		0.99(0.95-1.04)	0.88		
FBS		1.03(1.01-1.05)	<0.05*	0.99(0.96-1.02)	0.74
Cholesterol		1.03(1.01-1.04)	<0.001*		
Triglycerides		1.00(0.99-1.10)	0.40		
HDL		1.11(1.06-1.16)	<0.001*	0.92(0.79-1.07)	0.30
LDL		1.03(1.02-1.05)	<0.001*	1.04(0.99-1.09)	0.09
VLDL		1.01(0.97-1.05)	0.40		

DISCUSSION

Healthcare workers who work during the night face disruptions in their circadian rhythms including sleep disturbances and altered eating patterns. These factors potentially contribute to an increased risk of inflammation in the body. Proinflammatory markers like hsCRP indicate inflammation and elevated levels of these markers suggest inflammatory response in the body. In this study hsCRP was estimated in night shift healthcare workers and risk factors association with elevated hsCRP was analysed.

In our current study, the mean age of the control group was (29.5±9.00yrs) which is two years higher than the cases (27.89 6.57yrs). This may be because in a healthcare facility usually younger people are more exposed to night shift work, however, this difference was not statistically significant. Mean frequency of exposure to night shift was (8.15±2.39) days in a month with average exposure of (4.25±4.00) years.

There was no significant difference in BMI in both the groups. Similar findings were also seen in the study done by Buchvold et.al [12]. However, other studies (Di Lorenzo et. al. reported that obesity was more prevalent in shift workers (20%) compared to daytime workers (9.7%). Night shift work was associated with increased BMI regardless of age or duration of shift work exposure [13]. Waist circumference is an indicator of abdominal obesity. Our study revealed that the mean waist circumference in night shift healthcare workers was higher compared to the day shift workers. This result is in concordance with the study by Sun M et. al. where, they found that permanent night shift had highest odds ratio for abdominal obesity [14]. Night shift work schedule leads to desynchronization and loss of normal variation in metabolic hormones, like, insulin, cortisol and leptin which, disrupts the balance of energy metabolism and leads to increase in waist circumference. Besides shift work also causes change in lifestyle, sleep deficiency, decreased physical activity which can also be linked with increase in waist circumference [15].

SBP was significantly higher in night shift workers compared to day shift workers which is in accordance with the study by Yeom Han et al [15]. Blood pressure control is more difficult in shift workers which may be because of irregular light exposure, which is associated with deranged circadian rhythm and melatonin secretion [9]. Besides, night shift duty also increases sympathetic nervous system activity, increase in blood pressure and heart rate. Prolonged exposure to these factors may entrain the cardiovascular system to operate at an elevated pressure equilibrium through structural adaptations such as left ventricular hypertrophy [16].

Working in night shift disrupts the daily routine of an individual affecting normal food intake and exercise. In our study we found that, fasting blood sugar (FBS) was significantly higher ($p < 0.05$) in night shift healthcare workers. Similar findings were also reported by Loren Zo et al and Nagaya et al [13,17]. Blood glucose homeostasis is associated with central circadian rhythmicity as well as peripheral oscillators located in regions such as the liver, pancreas, muscles and white adipose tissue [17]. Adipose tissue plays an important role in the endocrine system. In addition to functioning as a fat depot, these tissues play a role in adipokine secretion, which is involved in several physiological pathways, including sugar and energy metabolism. Sleep deprivation also leads to decrease in glucose tolerance by affecting the cortisol levels and also it leads to insulin resistance. Hence, proper screening and intervention strategies in rotating night shift workers are needed for prevention of diabetes mellitus [18].

Furthermore, we found that serum total cholesterol and LDL cholesterol was significantly higher in night shift subjects. However, no difference was seen in serum TG levels. Serum HDL was found to be higher in night shift. Similar to our findings, Ghiasvand M et al and Rahmann AM et al found higher total cholesterol and LDL–C in night shift workers but TG, HDL was not correlated with shift work [19,20]. Furthermore, studies have shown that night workers who slept less than 7hrs per night faced higher risk of dyslipidemia [19,20]. The circadian clock is the key regulator of lipid metabolism therefore, periodic disruption of circadian rhythm negatively affects lipid metabolism promoting the development of atherogenic lipid profile [20].

In our study all the parameters for metabolic syndrome (waist circumference, SBP, FBS, lipid profile) were deranged in night shift healthcare workers suggesting night shift may increase the risk of metabolic syndrome in individuals. Circadian misalignment due to night shift has also been found to result in adverse metabolic and cardiovascular consequences, including a decrease in leptin, an increase in glucose and insulin, an increase in mean arterial blood pressure, and reduced sleep efficiency [21,22].

In our study, pro-inflammatory markers hsCRP and TLC were higher ($p<0.001$) in night shift healthcare workers, Kim et al also found increase in inflammatory markers in night shift workers of other professions [23]. S Puttonen et al in their study linked irregular working hours with increase in inflammatory markers. They even found out that night shift workers who moved to day shift work, inflammation was decreased pointing reversible effect of shift work on inflammation [23].

Chronic low-grade inflammation plays an important role in the development of cardiovascular diseases, regular follow up of inflammatory markers in night shift workers may serve as an early indicator in predicting effects of shift work on health [22]. Disruption of the circadian rhythm due to night shift work results in increase in cytokines hence increasing the levels of pro-inflammatory markers. hsCRP is a marker of systemic inflammation and it is now well accepted that inflammation has an important role in development of cardiovascular disease. Moreover, epidemiological studies have shown chronically elevated hsCRP predicts CVD [24]. Logistic regression analysis of hsCRP with various factors by both univariate and multivariate analysis was done except some of the variables where multivariate analysis cannot be done owing to multicollinearity. By univariate regression analysis it was seen that age, female gender and married persons are the risk factors for increase in hsCRP, but female gender and marital status were not found to be independent predictors for increase in hsCRP. Tang Y et al in their study showed that serum hsCRP increases with ageing. Ageing is thought to be related to the inflammatory processes [25]. Several cytokines IL-6, TNF and CRP increases with age in absence of acute infection. In the study done by Tang Y et al male persons had higher hsCRP compared to the female, which was in contradiction to our study [25]. This may be because gender was not equally distributed in our study group and had more female predominance.

Night shift work in healthcare personnel was found to be an independent risk factor for increase in hsCRP. Though frequency of night shift work per month and duration of night shift work since years were found to be risk factors for increase in hsCRP but they are not found as the independent predictors for increase in hsCRP. CJ Morris et al in their study found that there was 3-29% increase in inflammatory markers in night shift workers [26]. In our study, waist circumference was not found to be a risk factor for increase in hsCRP. Whereas higher BMI was found to be an independent risk factor for elevated hsCRP, which in turn is a risk factor for CVD.

Serum fasting blood sugar (FBS), serum cholesterol, serum LDL and HDL though found as the risk factor for elevated hsCRP but was not found as the independent predictor in our study. hsCRP is stimulated and produced in the liver by pro-inflammatory cytokines. Hence, elevated FBS is associated with increase concentration of hsCRP [27,28]. Epidemiological studies have also indicated that individuals with dyslipidemia are in a pro- inflammatory state with elevated levels of cytokines IL-6, TNF which are formed due to ongoing inflammation in artery stimulated by oxidized LDL leading to production of these cytokines hence increasing the expression of hsCRP [29].

LIMITATIONS:

In our study we were not able to obtain detailed personal histories which may have biased our study results. We had a greater percentage (53.85%) of nurses in our study group. So, with a larger sample size and proper segregation of health care workers it will provide much better results. The comparison within different groups of health care workers will be more insightful in identifying those groups who are at a greater risk of increase in proinflammatory markers and hence the CVD risk.

CONCLUSION

Proinflammatory markers (hsCRP, TLC) was higher in night shift health care workers. Female gender, marital status, frequency and duration of night shift was found as risk factors for increase in hsCRP but by multivariate regression analysis night shift work itself is found to be an independent predictor for increase in these proinflammatory markers. This increase is further aggravated with age and BMI. As hsCRP is a significant contributor of cardio-metabolic risk factor, it is important to identify and prevent the rise of these proinflammatory factors by regular follow up. Health workers must be counselled and made aware of different lifestyle interventions. Health organizations and systems should also promote and initiate strategies to prevent such occupational health hazards and enhance their performance. Further studies must be done to find risks in each vocational group in comparison to their mode of work and stress along with their personal and lifestyle factors which may together increase the risk of development of proinflammatory factors leading to increase in CVD risks.

CONFLICT OF INTEREST STATEMENT:

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS:

JB: Conceptualization, Methodology, Investigation, Writing - Original Draft. BA: Resources and Data curation. RS: Conceptualization, Investigation, Validation, Supervision, Writing - Original Draft. RAM: Resources and Data curation, MP: Data analysis. SM: Conceptualization, Resources. SRM: Formal analysis, Supervision, Final Review. All the authors read, reviewed, and revised the manuscript.

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DATA AVAILABILITY STATEMENT:

All data generated during the current study are available upon reasonable request sent to the corresponding author.

ETHICS STATEMENT:

Involvement of human participants in the current study were reviewed and approved by the Ethics Committee of KIMS (CDSCO Reg No : ECR/321/Inst/OR/2013/RR-20)(Reference: KIIT/KIMS/38/2019). Written informed consent for participation in this study was taken in accordance with the national legislation and the institutional requirements.

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FOOT NOTES:

BMI – Body mass index, SBP- Systolic blood pressure, DBP- Diastolic blood pressure, FBS- Fasting blood sugar, TG- Triglyceride, HDL- High density lipoprotein, LDL- Low density lipoprotein, VLDL- Very low-density lipoprotein, hsCRP- high sensitivity lipoprotein, TLC- Total leucocyte count

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