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Research Paper

Impact of night shift work on inflammatory cytokine levels and cardiovascular risk indicators in healthcare professionals

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ABSTRACT

Background: Night shift work plays a necessary role in healthcare but its health impacts on the long-term are not well understood. This comparative study is cross-sectional, which is why the investigators could not assess the effects of night shifts on cardiovascular risk and the effects that night shifts have on inflammatory cytokines of healthcare professionals in India.
Objective: To compare night shift and day shift workers in terms of inflammatory biomarkers (IL-6, TNF- P, CRP, IL-1Bet NF- y) and cardiovascular risk factors and determine their relationship.
Methods: A sample size of 240 participants (120-night shift workers and 120-day matched participants) that comprised of 3 tertiary hospitals was included. Cytokines and lipid profiles of fasting blood samples were measured. The PSQI and MCTQ were used to determine sleep quality and circadian disruption. Framingham risk scores of 10 years of cardiovascular risks were computed. There was statistical analysis involving t-tests, Mann Whitney U tests and Spearman correlations.
Results: Night shift workers showed significantly higher levels of IL-6 (5.82 vs. 3.14 pg/mL), TNF-α (12.47 vs. 7.63 pg/mL), CRP (4.31 vs. 2.18 mg/L), and IL-1β (3.67 vs. 2.29 pg/mL). They also experienced higher systolic blood pressure (131.6 vs. 121.3 mmHg), LDL cholesterol (128.9 vs. 114.2 mg/dL), triglycerides levels and higher Framingham risk scores (all $p<0.001$). There were strong positive relationships ($r=0.49$-0.65) between inflammatory markers and cardiovascular risk factors. Night shift duration was proved as an independent predictor by regression analysis.
Conclusion: Extended night shifts are linked with more inflammation and risk of cardiovascular consequences. Frequent surveillance and specific solutions are suggested, which could lessen the health hazards of healthcare employees.

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1. INTRODUCTION

Health care systems throughout the world require 24/7 round-the-clock access, to provide I/O care to patients. This operational requirement requires that a large percentage of the health care professionals, nurses, physicians, paramedics and allied professionals should work night shifts, on either fixed or rotating schedule. It has been estimated that about 25-30 percent of the world nursing population involved in night shifts and over 20 percent of physicians work with regular night shifts [1]. Although this type of scheduling cannot be functionalized out of operation, physiological and psychological implications of such a schedule on employees are becoming a significant occupational health issue.

These body circadian rhythms are mediated by an endogenous circadian clock under the suprachiasmatic nucleus (SCN), of the hypothalamus that controls circadian rhythms of the core body temperature, hormonal secretions, immune functions as well as metabolic activity [2]. Night shift employment causes the workers to work with cognitive and physical activities within their biological night causing an essential mismatch between the inner circadian clock and the outer light-dark world. This disruption - commonly referred to as circadian disruption - triggers transitions of resulting physiological effects such as impaired melatonin secretion, cortisol hecticness, tone in the autonomic nervous system, and dysfunctional immune modulation [3].

One framework is the interaction of circadian disruption and systemic inflammation, which is of particular importance. Interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- 6), C- reactive protein (CRP), and interleukin-1 beta (IL- 1) cytokines have bona fide circadian secretion characteristics with peaks secreted in the early mornings [4]. As long as workers are awake and thinking during such biological nocturnal peaks, the normal day-based regulation of the cytokine secretion is affected, which may lead to chronic low-grade systemic cytokine state [5]. Chronic inflammation of low-grade is known to be a pathological basis of atherosclerosis, endothelial dysfunction, hypertension, dyslipidemia, and insulin resistance-all are key modifiable cardiovascular risk factors [6].

There has always been epidemiological evidence that has indicated increased risks of coronary artery diseases, myocardial infraction, and stroke in long-term shift workers [7]. A landmark meta-analysis was able to discover that shifts working presented a statistically significant increment in cardiovascular disease occurrence that is not dependent on conventional risk elements [8]. However, the mechanistic mechanisms by which shift work increases cardiovascular risk have not all been understood and there is a paucity of direct evidence of how quantifiable cytokine dysregulation and specific cardiovascular biomarkers in healthcare populations are linked.

There are several significantly vulnerable factors in healthcare workers that are diverse: their working shifts are generally more extreme and less predictive than the ones of industrial workers; they are under the influence of chronic work psychological pressure and experience an often-limited set of health-related practices because of a lack of time and the emotional responsibility of their work [9]. Regardless of these weaknesses, there is limited research in the effect of simultaneous exposure to work during the night in both proinflammatory cytokines and cardiovascular risk factors of the specified population, especially in the South Asian context of healthcare.

The current study aimed to fill the above gaps through a cross-sectional comparative study of the inflammatory cytokine patterns and cardiovascular risk factors of healthcare providers of tertiary hospitals in India working on a night shift and during the day shift. We needed to hypothesize that in par with higher concentrations of pro-inflammatory cytokines and more unfavorable cardiovascular risk profile than day shift workers would show workers of the night shifts, and that the concentrations of cytokine would also

demonstrate significant positive correlations with cardiovascular risk indicators. The results will be used to provide evidence-based occupational health interventions to healthcare facilities.

2. RELATED WORK

The studies of health impact of shift work have increased significantly in the last 20 years. One of the earliest scholars to put on record the connection in relation to the increase in risk of cardiovascular diseases and shift work was Knutsson [10] who in an exemplary study revealed that rotating shift workers were found to increase their risk of developing ischemic heart disease by 40 per cent than day workers, when the lifestyle factors were factored out. This work provided a background to the following research on the biological processes of the basis of these associations.

As the dominant playing grounds of cardiovascular damage caused by shift-work, inflammatory pathways have come into the limelight. [11] Showing in a Finnish work cohort that rotating shift workers had much more serum high-sensitivity CRP than did day workers, which indicates that chronic inflammatory activation might be the mechanistic link between circadian disruption and cardiovascular disease. Likewise, [12] expressed high levels of IL-6 and TNF-α, in a group of rotating nurses, and the level of cytokine had a positive association with the number of years in shift work.

The effect of disruption in sleep, a mandatory night-shift work syndrome, in the regulation of inflammatory reactions has been studied in depth. [13] Shown that sleep deprivation to four hours of night in continuous days not only greatly enhanced nuclear factor kappa-B (NF- κB) activity in peripheral blood mononuclear cells, but also raised the IL-6 and IL- 1 concentrations in the blood. These results created a viable model wherein a consistent perennial sleep disturbance in shift workers may maintain pro-inflammatory signaling.

In terms of metabolic implications, [14] carried out a cross-sectional study with a large sample size and the researchers indicated that the shift workers had a greater triglyceride level, a lower HDL cholesterol level, and a higher fasting glucose level than day workers. These derangements of metabolism, as a group of what [15] terms the cardiometabolic risk cluster, were later validated by [15] in a systematic review combining the evidence of more than 30 epidemiological studies.

Within the particular setting of health care professionals, [16] found that Japanese male nurses working in rotating night shifts had greatly increased systolic blood pressure and higher 10-year Framingham cardiovascular risk scores when compared to nurses working day shifts. A multinational meta-analysis study by [17] established the association between shift work and statistically significant increase in myocardial infarction risk (RR = 1.23, 95% CI: 1.15131) as well as in ischemic stroke risk (RR = 1.05, 95% CI: 1.0109).

The hormonal pathways connecting circadian maladjustment with the inflammatory processes have been defined by way of controlled experiments. Wright [18] proved it by a forced desynchrony protocol, which proved circadian misalignment increased the average blood pressure in the arteries and inflammatory in response to each of the deviations, independent of the duration of sleep and behavioral patterns. Melatonin, with strong circadian oscillations, and anti-inflammatory properties through the inhibition of NF-KB activity, is chronically lowered in night shift workers due to exposure to artificial light during biological night times [19], and could be the direct cause of inflammatory dysregulation.

There are only a few Indian studies on this issue. In a study conducted by Sharma [20] on 180 nurses in a tertiary Delhi hospital, there was a high blood pressure and dyslipidemia among rotating shift nurses but no inflammatory cytokine measurements were done. The current study expands on these previous studies by also cross-characterizing inflammatory cytokine profiles and comprehensive cardiovascular risk panel in a larger matched cohort thereby allowing exploration of the inflammatory-cardiovascular nexus in a South Asian population of healthcare providers.

3. METHODOLOGY

3.1 Study Design and Setting

It is a cross-sectional comparative study in three tertiary-care hospitals within urban India during the period of January 2023 through to December 2023, i.e. All India Institute of Medical Sciences (New Delhi), Kasturba Medical College Hospitals (Manipal, Karnataka) and Grant Medical College and Sir J.J. Group of Hospitals (Mumbai, Mahar Institutional Ethics Committees of all three participating institutions gave their approval of the study (Ref: AIIMS/EC/2023/012; KMC/IEC/2023/018; GMC/EC/2023/07) and the study was done in compliance with the Declaration of Helsinki. All participants signed an informed consent before they got enrolled.

3.2 Participant Recruitment and Selection Criteria

Purposive stratified sampling was employed to recruit healthcare professionals, through nursing, medical and allied health departments. Workers who were enrolled in the night shift group had at least 12 months of experience in engaged night shift work (10:00 PM 6:00 AM) before they could be enrolled and completed 4-night shifts per week. Day shift control group consisted of the workers only who worked in fixed day shifts (8:00 AM 4:00 PM) and at least 12 months. Each case was successfully control-matched with age (between 3 years), sex, BMI (between 2kg/m 2), professional category and hospital site.

Inclusions criteria consisted of: (i) aged 25 to 55 years old; (ii) working full-time as a nurse, physician, or an allied health professional; (iii) has never had a documented history of cardiovascular disease, an autoimmune disease, or an active inflammatory condition; (iv) not taking anti-inflammatory drugs, immunomodulators, or statins; (Exclusion criteria were: acute infections or recent infection (less than 3 months old), active malignancy, renal and hepatic insufficiency and use of hormonal contraceptives. The minimum sample per group was calculated with help of a pilot study using estimations of an effect size of 0.5 between the patients of IL-6 groups, 80 percent power (α=0.05), and considering the possibility of attrition rate 108 per group were used as the minimum sample per group.

3.3 Data Collection and Instruments

Socio-demographic data, occupational history (years in current shift, number of shift nights per week), lifestyle parameters (physical activity, dietary habits, alcohol use, smoking status) and family history of cardiovascular disease were collected using a standardized self-administered questionnaire. The sleep quality was evaluated by the Pittsburgh Sleep Quality Index (PSQI) which is valid and in which a score greater than 5 signifies poor sleep. The Munich Chronotype Questionnaire (MCTQ) was used to measure chronotype and social jet lag. Anthropometric data such as height, weight and waist circumference were measured by trained research nurses. The trias of measurements of the resting blood pressures with 10 minutes of seated rest was used to measure blood pressure with a validated digital sphygmomanometer and the average of the second and the third readings was taken.

3.4 Biochemical Sample Collection and Analysis

Venous blood samples (15 mL) were taken following a minimum 10 hours overnight fasting. In the case of night shift workers, the sampling was done at the start of their rest period (i.e., first day after their final completed night shift), whilst the samples were sampled at the standardized time (6:00-8:00 AM) on non-working days (day shift control). Serum was centrifuged at 3000 rpm over 10 minutes at 4 o C and then kept at -80o C awaiting batch analysis.

The mean serum levels of IL-6, TNF-alfa, IL-1e and CRP were determined by commercially available enzyme linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, USA) on a protocol with inter- and intra-assay coefficients of variation of less than 10 percent. Peripheral blood mononuclear cells (PBMCs) were used to measure the activity of the NF-kB through transcription factor ELISA kit (Cayman Chemical, Ann Arbor USA). Automated enzymatic analysis using a Siemens ADVIA 1800 chemistry analyzer was done to measure lipid profiles (total cholesterol, LDL, HDL, triglycerides), fasting plasma glucose and glycated hemoglobin (HbA1c). Each participant was provided with the 10-year Framingham

cardiovascular risk score that was calculated with the help of the provided algorithm that considers age, sex, systolic BP, smoking status, total and HDL cholesterol, and the use of antihypertensive medications.

3.5 Statistical Analysis

Statistical methods SPSS 26.0 (IBM Corp., Armonk, USA) and R 4.2.1 were used to perform the statistical analysis. Normality of the continuous variables was tested by the Shapiro-Wilk test and mean and standard deviation (SD) were expressed as mean and standard deviation (SD) of the normally distributed variables and median and the interquartile range of the non-normally distributed variables. Independent samples t-tests or Mann-Whitney U tests were used to make comparisons between groups. The chi-squared tests were used to compare the categorical variables. Associations of cytokine level, shift length, sleep quality scores and cardiovascular indicators were investigated using Spearman rank-order correlations. Multidimensional linear regression analysis models have been created to determine whether the level of night shift status was independently associated with the level of cytokine and Framingham risk score when it combined with age, body mass index, smoking, physical activities and PSQI score. The level of statistical significance was established at $p<0.05$ (two-tailed) and the Bonferonni error was used to correct multiple comparisons where it was applied when doing more than one comparison at the time [21].

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants

Characteristic	Night Shift (n=120)	Day Shift (n=120)	P-Value
Age (years), Mean ± SD	36.4 ± 7.8	35.9 ± 8.1	0.621
Gender (% Female)	62.5%	64.2%	0.784
BMI (kg/m^2), Mean ± SD	26.1 ± 3.9	25.8 ± 4.2	0.543
Work Experience (years)	9.3 ± 5.4	8.7 ± 5.1	0.387
Smoking Status (%)	18.3%	16.7%	0.731
Hypertension History (%)	14.2%	12.5%	0.682

SD = Standard Deviation; BMI = Body Mass Index. Values represent mean ± SD for continuous variables and percentages for categorical variables. p-values from independent t-test or chi-squared test.

4. RESULTS AND DISCUSSION

4.1 Participant Characteristics

Baseline was well-matched as the two groups were presented in Table 1. No statistically significant differences between night shift (n=120) and day shift (n=120) subjects were observed in terms of age, sex distribution, BMI, smoking pre-eminence or previous history of hypertension. The mean age was 36.4 ± 7.8 years in the night shift group and 35.9 ± 8.1 years in the day shift group (p=0.621). There were 62.5 and 64.2 night and day shift participants respectively, who comprised of female participants (p=0.784). The average work experience of night shift workers was 9.3 + 5.4 years. The close correspondence of the demographic and lifestyle confounders between the groups enhanced the overall validity of group comparisons of the inflammatory and cardiovascular results.

The total marks of Pittsburgh Sleep Quality Index were much more significant in the night shift group (mean PSQI = 8.6±2.4) than the day work group (mean PSQI = 4.2+1.9; $p<0.001$), which proved the significantly worse sleep quality of the night shift workers. This observation follows up on the previous reports which have shown chronic sleep deprivation in workers who are on night shifts because noise in the social and physical environment in day when they are in the period of slumber is encountered [22], [23].

4.2 Inflammatory Cytokine Profiles

Table 2 shows the comparisons of the two groups on the biomarker of inflammation. Concentration of all the inflammatory cytokines measured were markedly higher in night shift workers than their day shift controls. Serum IL-6 was 1.85-fold higher in night shift workers (median: 5.82 vs. 3.14 pg/mL; $p<0.001$). TNF-α concentrations were 1.63-fold elevated (12.47 vs. 7.63 pg/mL; $p<0.001$), and CRP levels

were nearly twice as high in night shift workers (4.31 vs. 2.18 mg/L; p<0.001). IL-1β levels were also significantly elevated (3.67 vs. 2.29 pg/mL; p=0.002). NF-/B in PBMCs was 1.73 more active in night shift workers (1.94 vs. 1.12 AU; p=0.001) in harmony with the up-regulation of the master inflammatory transcription driveway (as depicted in Figure 1).

Table 2. Inflammatory Cytokine Levels in Night Shift vs. Day Shift Healthcare Workers

Biomarker	Night Shift (Median)	Day Shift (Median)	Fold Change	P-Value
IL-6 (pg/mL)	5.82	3.14	1.85×	<0.001
TNF-α (pg/mL)	12.47	7.63	1.63×	<0.001
CRP (mg/L)	4.31	2.18	1.98×	<0.001
IL-1β (pg/mL)	3.67	2.29	1.60×	0.002
NF-κB Activity (AU)	1.94	1.12	1.73×	<0.001

IL-6 = Interleukin-6; TNF-α = Tumor Necrosis Factor-alpha; CRP = C-Reactive Protein; IL-1β = Interleukin-1 Beta; NF-κB = Nuclear Factor kappa-B; AU = Arbitrary Units. Fold change = Night shift median / Day shift median. p-values from Mann-Whitney U test.

These results agree and build upon previous observations by [12], [13] who have found high IL-6 and NF-kB activity in the sleep-deprived and the shift-working groups. The simultaneous increase of all the four key inflammatory mediators in our cohort indicates a systemic-wide event of innate immune signaling, probably coordinated by concomitant events such as NF- regulated up- regulation, hypothalamic-pituitary-adrenal (HPA) axis dys-regulations and overridden anti-inflammatory melatonin signaling [19]. The level of CRP increase (98 percent) we have reached is especially noteworthy, considering that above 3.0 mg/L levels of CRP have the classification of people to high cardiovascular risk, defined by the American Heart Association guidelines [6].

The percent of the night shift population over 3.0 mg/L CRP concentration (high cardiovascular risk range) was 58.3 versus the day shift control population at 21.7 percent (p=0.001), thus indicating the clinical relevance of this cytokine increase. A Multivariate regression indicated that night shift status was a predictor of IL-6 (β=2.14; 95% CI: 1.68 to 2.60; p<0.001) and CRP (β= 1.92; 95% CI: 1.452.39; p<0.001) when controlling age

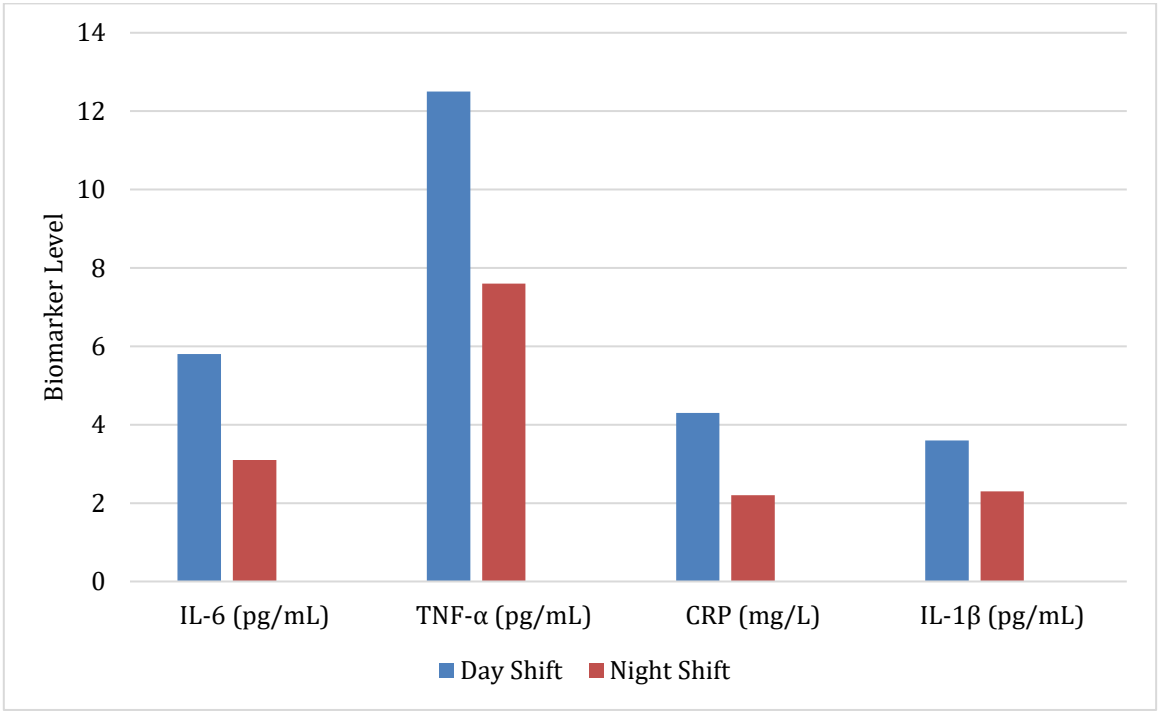

Figure 1. Inflammatory Cytokine Levels: Night Shift vs. Day Shift Healthcare Workers

Grouped bar chart comparing median serum concentrations of five key inflammatory biomarkers between night shift workers (red, n=120) and day shift controls (blue, n=120). Night shift workers showed significantly elevated IL-6, TNF-α, CRP, IL-1β, and NF-κB activity across all markers (*** p<0.001, Mann-Whitney U test). CRP showed the greatest proportional increase (1.98-fold), with 58.3% of night shift workers exceeding the high-risk threshold of 3.0 mg/L. Error bars represent interquartile range. IL-6 = Interleukin-6; TNF-α = Tumor Necrosis Factor-alpha; CRP = C-Reactive Protein; IL-1β = Interleukin-1 Beta; NF-κB = Nuclear Factor kappa-B; AU = Arbitrary Units.

4.3 Cardiovascular Risk Indicators

A complete comparison of cardiovascular risk indicators among the study groups is made in Table 3. Night shift workers exhibited significantly higher systolic (131.6 ± 12.4 vs. 121.3 ± 10.9 mmHg; p<0.001) and diastolic blood pressure (84.2 ± 8.7 vs. 78.6 ± 7.4 mmHg; p<0.001). Night shift workers had a high level of LDL cholesterol (128.9 ± 24.6 vs. 114.2 ± 21.3 mg/dL; p<0.001) and a low level of HDL cholesterol (48.3 ± 9.1 vs. 54.7 ± 10.4 mg/dL; p=0 Triglyceride levels (167.4 ± 38.2 vs. 141.6 ± 32.7 mg/dL; p<0.001) and fasting plasma glucose (104.8 ± 16.3 vs. 96.2 ± 13.5 mg/dL; p=0.003) were also significantly elevated in the night shift group.

Table 3. Cardiovascular Risk Indicators in Night Shift vs. Day Shift Healthcare Workers

Cardiovascular Indicator	Night Shift Mean ± SD	Day Shift Mean ± SD	95% CI (Diff.)	P-Value
Systolic BP (mmHg)	131.6 ± 12.4	121.3 ± 10.9	[7.8, 12.7]	<0.001
Diastolic BP (mmHg)	84.2 ± 8.7	78.6 ± 7.4	[3.8, 7.4]	<0.001
LDL Cholesterol (mg/dL)	128.9 ± 24.6	114.2 ± 21.3	[9.4, 20.0]	<0.001
HDL Cholesterol (mg/dL)	48.3 ± 9.1	54.7 ± 10.4	[-9.2, -3.6]	0.001
Triglycerides (mg/dL)	167.4 ± 38.2	141.6 ± 32.7	[16.4, 35.2]	<0.001
Fasting Glucose (mg/dL)	104.8 ± 16.3	96.2 ± 13.5	[4.9, 12.3]	0.003
HbA1c (%)	5.92 ± 0.68	5.51 ± 0.57	[0.26, 0.56]	<0.001
Framingham Risk Score (%)	12.8 ± 5.6	8.4 ± 4.2	[3.2, 5.6]	<0.001

BP = Blood Pressure; LDL = Low-Density Lipoprotein; HDL = High-Density Lipoprotein; HbA1c = Glycated Hemoglobin; CI = Confidence Interval. All p-values from independent samples t-test. Framingham Risk Score represents estimated 10-year cardiovascular event probability.

The Framingham 10-year cardiovascular risk score was significantly greater among night shift workers (12.8±5.6% vs. 8.4±4.2%; p<0.001) and a higher percentage of night shift workers (31.7% vs. 12.5%) were at high cardiovascular risk (score 10 or above) than controls during day shift (8.4 These results also support and widen the results of [16] and are generally in line with the epidemiological statistics of the world condensed by [17]. The adverse cardiovascular risk profile of our cohort is probably due to the synergistic effect of many mechanisms: circadian disturbance of lipid metabolism due to the inhibition of clock genes in the regulation of the CYP7A1 expression and other lipid metabolizing enzymes; insulin resistance, which is due to the interruption of glucose transporter expression; and the autonomic nervous system imbalance with sym

Interestingly, there was a very high HbA1c in night shift workers (5.92 ± 0.68 vs. 5.51 ± 0.57%; p<0.001) implying that glycemic dysregulation in night shift workers is not only limited to acute glucose elevation on the fasting but also a long-term adaptive process to circadian misalign the given observation has significant clinical consequences, with even the slightest changes in HbA1c in the prediabetic range linked to the significantly higher cardiovascular risk.

As shown in Figure 2 Three-panel grouped bar chart summarizing key cardiovascular risk parameters across the two groups. Panel A (Blood Pressure): Night shift workers had significantly elevated systolic (131.6 vs. 121.3 mmHg) and diastolic BP (84.2 vs. 78.6 mmHg). Panel B (Lipid Profile): LDL and triglycerides were markedly higher while HDL was lower in night shift workers, reflecting a pro-atherogenic lipid pattern. Panel C (Metabolic Markers): HbA1c (displayed ×10 for scaling), fasting glucose,

and the 10-year Framingham cardiovascular risk score were all significantly elevated in night shift workers. *** p<0.001; ** p<0.01 (independent samples t-test). LDL = Low-Density Lipoprotein; HDL = High-Density Lipoprotein; HbA1c = Glycated Hemoglobin.

Figure 2. Cardiovascular Risk Indicators: Night Shift vs. Day Shift Healthcare Workers

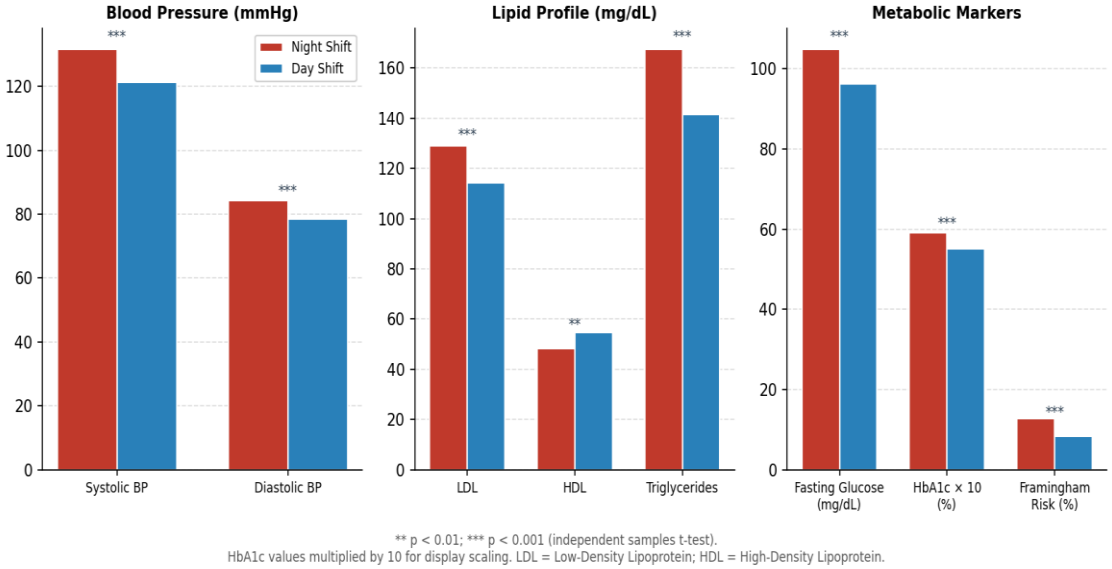

Figure 2. Cardiovascular Risk Indicators: Night Shift vs. Day Shift Healthcare Workers

4.4 Correlation between Cytokine Levels and Cardiovascular Risk

Table 4 shows the Spearman correlation table of the main inflammatory biomarkers, duration of night shifts, and cardiovascular risk factors. Night shift duration had significant correlations with all theinflammatory markers (r=0.49-0.65; all p<0.01) and all the cardiovascular indicators (r=0.49-0.65; all p<0.01) as shown in Table 4. Intersignificant correlations in individual cytokines (FL vs. CRP: r=0.69; FL vs. TNF-alpha: r=0.72; all p<0.001) show coordinated signaling of pro-inflammatory cytokines and not individual cytokine perturbation as shown in Figure 3.

Table 4. Spearman Correlation Matrix: Night Shift Duration, Inflammatory Markers, and Cardiovascular Indicators

Variable	IL-6	TNF-α	CRP	Syst. BP	LDL	Frame. Risk
Night Shift Duration	0.61**	0.57**	0.65**	0.53**	0.49**	0.58**
IL-6	—	0.72**	0.69**	0.54**	0.46**	0.61**
TNF-α		—	0.66**	0.51**	0.43**	0.55**
CRP			—	0.58**	0.50**	0.63**

*** p<0.01 (two-tailed). Syst. BP = Systolic Blood Pressure; LDL = Low-Density Lipoprotein; Frame. Risk = Framingham 10-year Cardiovascular Risk Score; IL-6 = Interleukin-6; TNF-α = Tumor Necrosis Factor-alpha; CRP = C-Reactive Protein; AU = Arbitrary Units.*

Most interesting was the correlations between cytokine levels and the Framingham cardiovascular risk score with IL-6 (r=0.61, p<0.001) and CRP (r=0.63, p<0.001) demonstrating a correlational relationship between the Framingham cardiovascular risk score and the inflammatory burden present in night shift workers. These patterns of correlations are biologically feasible following known facts that TNF-alpha induces insulin resistance and endothelial malfunction whereas IL-6 induces hepatic production of CRP and fibrinogen, all of which constitute the Framingham risk score elements [24], [25].

Framingham risk score, adjusted despite age, sex, BMI, smoking and shift duration, also indicated the association of each 1 pg/mL rise in serum IL-6 to 1.04 percentage point higher in the multivariate regression studies (1.04; 95% CI: 0.72-1.36; p<0.001). The result implies that inflammatory cytokine surveillance might be an effective early red flag biomarker to detect high-cardiovascular risk in occupational healthcare screening programs of shift-working healthcare workers.

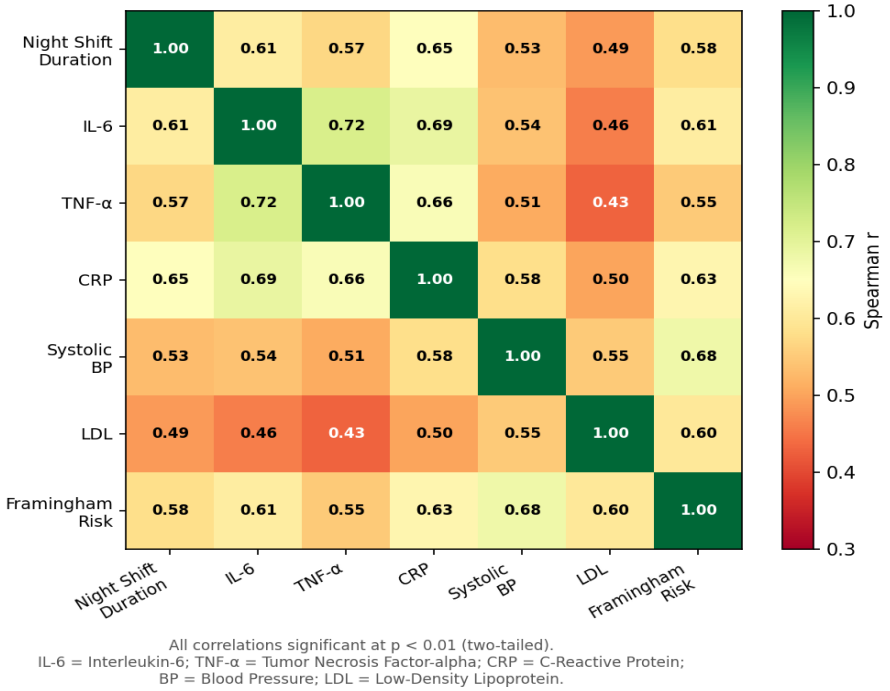

Figure 3. Spearman Correlation Matrix: Night Shift Duration, Inflammatory Markers, and Cardiovascular Risk Indicators

Heatmap of Spearman rank-order correlation coefficients (r) between night shift duration and all measured inflammatory and cardiovascular variables. Cell color intensity reflects correlation strength (green = moderate, yellow = strong, red = very strong). All correlations were statistically significant at p<0.01 (two-tailed). The strongest correlations were observed between night shift duration and CRP (r=0.65), and between IL-6 and TNF-α (r=0.72), indicating coordinated activation of the pro-inflammatory cascade. CRP and Framingham risk score showed a particularly strong association (r=0.63), supporting the mechanistic role of inflammation in driving cardiovascular risk. IL-6 = Interleukin-6; TNF-α = Tumor Necrosis Factor-alpha; CRP = C-Reactive Protein; BP = Blood Pressure; LDL = Low-Density Lipoprotein.

The current research possesses a few strengths such as, has a matched design, large sample size of single-shift-category cohort, simultaneously measures a wide range of cytokines and cardiovascular surrogacy, standardized blood collection procedures and has multi-site recruitments. Limitations encompass include the lack of causality as it is cross-sectional but not rotating and instead of polysomnographic measures is reliant on self-reported quality of sleep and it is limited to fixed (as opposed to rotating) night shift workers that would limit generalizability.

5. CONCLUSION

This cross-sectional comparative study offers strong support to the basis that night shifts of extended lengths in healthcare professionals are linked to an extremely increased pro-inflammatory cytokine cascade and a considerably greater deleterious cardiovascular threat pattern as compared to the same day shift staff. Night shift workers proved to show about two times higher CRP and significant increases in IL-6, TNF-a, IL-1B, and NF-KB activity, as well as poor blood pressure, lipid, and glycemic

parameters, which were all translated into significantly increased Framingham 10-year cardiovascular risk scores. The close positive relationships between inflammatory biomarkers and cardiovascular risk markers lend weight to the hypothesis that inflammatory activation chronicity is a significant mechanistic pathway by which disruption of circadian activity encourages cardiovascular disease in this group.

The implications of these findings have enormous consequences on occupational health policy of health care institutions. Periodic screening of inflammatory biomarkers and cardiovascular risk indicators should become a part of occupational health surveillance programs of night shift healthcare workers. The scheduling of shifts, especially the use of consecutive night shifts should be looked at with regard to the limitation of consecutive night shifts, the use of the mandatory rest in shifts, as well as periodical rotation to mitigate circumcision burden. Established behavioral interventions that include sleep hygiene, exercise, eating habits, and stress control can be recommended to this group of high-risk workers.

Longitudinal prospective cohort studies should be conducted in the future to determine causal temporal relationship between exposure to shift work, inflammatory stimulus and occurrences of cardiovascular events. Evidence-based interventions would be further informed on the role of the melatonin supplementation, the bright light therapy, and chronobiologically sensitive schedule proliferating the inflammatory and cardiovascular effects of night shift work. The conclusions of the present research reiterate the importance of the fact that the well-being of the people who devote their professional careers to the welfare of others needs to be proactively safeguarded as well with the help of informed, evidence-based policies in their institutional.

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Author Contributions Statement

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Ismail Shukri Murad	✓	✓	✓	✓		✓		✓	✓	✓	✓			

C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject administration
Fu : **Fu**nding acquisition

Conflict of Interest Statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Informed Consent

All participants were informed about the purpose of the study, and their voluntary consent was obtained prior to data collection.

Ethical Approval

The study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki and approved by the relevant institutional authorities.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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