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Prevalence of Infection in Patients Having Chills during Haemodialysis

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ABSTRACT

Background: Globally, a large population of End-Stage Renal Disease (ESRD) patients undergo hemodialysis (HD) as a treatment modality. The second most common cause of death in such patients in the presence of concurrent infections. The presence of chills, as an intradialytic complication, was studied as a marker of underlying infection in HD patients, confirmed by the neutrophil-to-leukocyte ratio (NLR). **Methods:** This cross-sectional, analytical study included 140 patients, aged 18 and above on maintenance HD. They were stratified into Group A (n=70), those who experienced chills during HD and Group B (n=70), which included age and gender matched individuals who had an uneventful HD. Demographics, co-morbidities and access site was recorded for each patient, followed by an extraction of a 2ml blood sample upon which the NLR was calculated. A value of ≥ 3.5 was the cutoff for a raised NLR. Data was entered and analyzed using SPSS v25. **Results:** Patients of Group A and Group B had a mean age of 55.0 ± 11.3 years and 53.2 ± 14.2 years (p=0.407), respectively, and included 37 (58.7%) males and 26 (41.3%) females. Amongst Group A (cases, with chills), 40 (57.1%) subjects had a raised NLR, as compared to 24 (34.3%) from Group B (controls), which was a statistically significant result (p=0.00664). Overall, hypertension was the predominant comorbidity, however, IHD was significantly more prevalent amongst cases (p=0.013). Tunneled catheter was the more prevalent access site in 38 patients (54.3%) (p=0.000027) who experienced chills. AVF was the prevalent access site for the control group (< 0.00001). **Conclusion:** The presence of chills in ESRD patients on maintenance HD is significantly associated with a raised NLR. In addition, most patients who experienced chills and simultaneously had a raised NLR were those in whom the access site was either a tunneled or non-tunneled catheter. Hence, recognition of chills in parallel to a raised NLR can warrant a clinician to prompt medical management and explore for not just access site associated but other occult sources of infection.

Keywords: Chills, Bacteremia, Hemodialysis, Neutrophil-To-Lymphocyte Ratio.

INTRODUCTION

End-stage renal disease (ESRD) is now a burden on public health, globally.[1] Hemodialysis (HD) is the commonest treatment modality with about 90.6% of ESRD patients receiving it.[2] With such a large population of patients undergoing hemodialysis, it is essential to be aware of the disease and treatment associated complications, especially intradialytic complications.

ESRD patients owing to their immunocompromised state are susceptible to infections, which is the second leading cause of death following cardiovascular events in HD patients.[3,4] One of the manifestations of ongoing infections in HD patients can be chills, which have a reported occurrence of up to 40% (with or without fever) during HD sessions.[5] However, in order to identify chills as a marker of infection, there has to be a confirmatory parameter to prove ongoing infection in parallel.

The neutrophil-to-lymphocyte ratio (NLR) is an extensively studied parameter signifying systemic inflammation in various clinical settings.[6,7] This study was carried out to evaluate the reliability of chills as a marker of ongoing infection confirmed by the NLR. Keeping in mind that while the presence of infection in the setting of inflammation is incidental, inflammation is usually present if there is an infection, making NLR an efficient tool.

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MATERIALS AND METHODS

After approval by the Ethics Review Committee, a cross-sectional, analytical study was conducted over 6 months, from January to June 2020 at a 13-bedded Hemodialysis Unit at Combined Military Hospital, Lahore. The unit has an average influx of 45 ambulatory patients per day, and an average of 100 patients registered for maintenance hemodialysis per month.

All patients aged 18 and above with ESRD, undergoing maintenance hemodialysis (for at least

one month) participated in the study after seeking informed consent, via a non-probability, consecutive sampling technique. Patients on dialysis for acute kidney injury (AKI), patients with a history of leukemias/other malignancies, and those already on antibiotic therapy were excluded from the study. Patients who were experiencing chills before the HD started, those with an ongoing blood (or blood products) transfusion during the HD, or those with a known heparin allergy were also excluded to reduce confounding factors that can lead to chills. Those patients who had been taken as a case or control once were not included again, regardless of the presence of chills in a later session.

All patients who met the criteria were monitored during the HD sessions for the intradialytic complication i.e. chills. Patients who were identified with chills either during the HD or immediately after the session (i.e., within one hour), were included as cases and named Group A. For every patient with chills, an asymptomatic patient age (within 5 years) and gender-matched, with an uneventful dialysis session was added to the control group, named Group B.

Data including demographics, co-morbidities, and access site (tunneled catheters, non-tunneled catheters or arteriovenous fistulas (AVF)) was recorded. For all patients, a 2 ml blood sample was drawn from the arterial line of the extracorporeal HD circuit into a vial containing edetate dipotassium. The sample was sent to the laboratory for analysis of the complete blood count, including the differential leukocyte count (DLC). The neutrophil-to-lymphocyte count ratio (NLR) was calculated using the DLC. NLR values of ≥ 3.5 were considered as raised.[8]

Moreover, all the laboratory investigations were done under the supervision of an expert pathologist using the same standard laboratory equipment (automated analyzer Sysmex KX 21). In a single dialysis session, a standard blood flow of 250ml/min was set for all patients. A synthetic hemodialyzer at room temperature was used which was discarded after each use and lastly, and only the machines with functional thermostat were operated.

All data was entered and analyzed using SPSS v25 for relevant statistical tests of significance at a 95% confidence interval and p-values were considered significant if less than or equal to 0.05. Descriptive statistics were drawn for continuous data and inferential statistics determined for various features of the two groups. Demographic characteristics and other continuous data were presented as means and standard deviations. The Chi-square test was used to compare nominal data, and the Mann-Whitney U test was used for the comparison of NLR.

RESULTS

The 140 patients included in the study were divided into two groups, Group A, cases (n=70) and Group B, controls (n=70) who had a mean age of 55.0 ± 11.3 years and 53.2 ± 14.2 years (p=0.407), respectively. Within Group A, cases with an NLR of ≥ 3.5 had a mean age of 58.3 ± 9.9 years which was significantly older than those with a low/normal NLR (p=0.011) as shown in [Table 3]. Both groups had 37 (58.7%) males and 26 (41.3%) females.

Table 1: Frequency of co-morbidities and vascular access sites amongst Group A and B

	Group A – Cases n = 70		Group B – Controls n = 70		P-value
	Frequency	Percentage	Frequency	Percentage	
Diabetes mellitus	40	57.14%	34	48.57%	0.310
Hypertension	56	80%	56	80%	1.00
Ischemic Heart Disease	21	30%	9	12.86%	0.013
Smoking	18	25.7%	10	14.29%	0.144
Tunneled catheters	38	54.29%	14	20%	0.000027
Non Tunneled catheters	15	21.42%	9	12.86%	0.178467
AVF	17	24.28%	47	67.4%	< 0.00001

Table 2: Comparison of NLR groups amongst Group A and B

	Group A – Cases (n = 70)			Group B – Controls (n = 70)		
	< 3.5 (n = 30)	≥ 3.5 (n = 40)	p-value	<3.5 (n = 46)	≥ 3.5 (n = 24)	p-value
Age	51.3 ± 12.5	58.3 ± 9.9	0.0111	52.2 ± 14.7	54.17 ± 12.0	0.547
Diabetes mellitus	20	20	0.163	19	15	0.092
Hypertension	28	28	0.0157	34	22	0.078
Ischemic Heart Disease	8	13	0.598	6	3	0.949
Smoking	6	12	0.678	8	2	0.304
Non-tunneled	17	21	0.729	6	8	0.043
Tunneled	6	9	0.801	8	1	0.117
AVF	7	10	0.872	32	15	0.550

Hypertension was the predominant comorbidity overall, precisely 80% amongst both cases and controls (p=1.0), however, IHD was significantly more prevalent amongst cases (p=0.013). Tunneled catheter was the more prevalent access site in 38 patients (54.3%) (p=0.000027) who experienced chills. AVF was the prevalent access site for the control group (< 0.00001). A higher number of

patients experienced chills for all types of access sites with a raised NLR, nonetheless, this difference fell out of statistical significance [Table 3].

When the sample population was divided into groups based on an NLR <3.5 (low/normal) and an NLR ≥ 3.5 (raised) amongst cases and controls and the results were as shown in [Table 3]. Lastly, patients who experienced chills had a higher NLR as compared to the controls (p=0.00664).

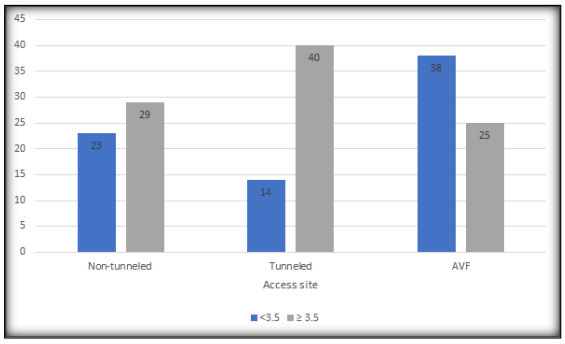

Figure 1: Frequency of patients with various vascular access sites amongst patients with NLR less than and more than/equal to 3.5

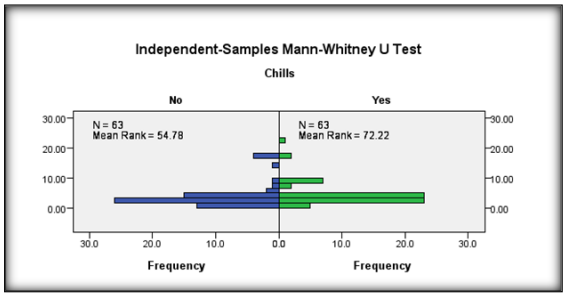

Figure 2: Mann-Whitney U Test showing non-normal distribution of NLR data between Groups, A and B

DISCUSSION

We conducted this study with the goal of evaluating chills as a clinical sign that could signify an ongoing infection in ESRD patients on HD, by keeping NLR as the diagnostic indicator. We discovered that there was a statistically significant correlation between a raised NLR (≥ 3.5) and the occurrence of chills during HD (p=0.00664).

Clinically, some commonly used inflammatory markers are: presence of fever, C-reactive protein (CRP) levels, blood cultures and procalcitonin levels, however, we used NLR for the following reasons. To start with, the presence or absence of fever can be misleading in ESRD patients and temperature is not a specific marker for infection in such patients.[9] Furthermore, C-reactive protein (CRP) and other acute phase reactants have unreliable reference values in dialysis patients.[10] Although, blood cultures have long been the most accurate and conclusive method, the time consuming nature of the test, delayed time to positivity and its tendency to be affected by antibiotic usage render it infeasible as an early detector of infections.[11] Lastly, absolute procalcitonin, a marker of acute bacterial infection, also has a limited role in identifying infection in hemodialysis patients.[12] This makes NLR a cost effective and reliable interpreter of ongoing infection in such patients.

Patients on HD have three methods of access to the circulatory system, namely, tunneled catheters, non-tunneled catheters and AVF. Catheters can be a source of catheter-related bloodstream infections, exit-site infections and tunnel infections, all of which lead to increased rates of hospitalizations and adverse outcomes.[13] In another study by M. Miller et al., an episode of chills was the most common clinical sign found in 60-80% patients who had catheter-associated infections proven by positive blood cultures.[14] This is backed by our study, as a higher number of patients who experienced chills had tunneled catheters and non-tunneled catheters as the access site. In addition, a study by Shepshelovich et al.[15] identified possible causes of infection in a sample of 162 patients amongst which the largest number (73) of patients had vascular catheter associated infections, along with other notable causes including urinary tract infections, pneumonia, and infective endocarditis.

This association is further strengthened by the fact that we excluded patients with fever and other noticeable signs of infection, along with confounding factors that could cause chills in order to isolate chills as an independent marker of ongoing infection. Hence, recognition of chills in parallel to a raised NLR can warrant a clinician to prompt medical management and explore for not just access site associated but other occult sources of infection. This can also help in devising guidelines for infection prophylaxis in ESRD patients on maintenance HD who experience chills.

However, there were certain limitations to the study design. Both the small sample size and the conductance of the study in only one HD unit limit the generalizability of the results. Moreover, there can be other non-infective causes of a pyrogenic reaction, although we did try to minimize this bias as much as possible by having a stringent exclusion criteria. Lastly, patients taking drugs that may cause neutrophilic leukocytosis and hence, alter the NLR such as steroids or lithium weren't accounted for.

CONCLUSION

The presence of chills in ESRD patients on maintenance HD is significantly associated with a raised NLR. In addition, most patients who experienced chills and simultaneously had a raised NLR were those in whom the access site was either a tunneled or non-tunneled catheter. This suggests that the occurrence of chills during HD can indicate ongoing catheter-associated infections along with other apparent and occult infections. Our research

establishes that there is a need for further diagnostic investigations or empirical treatment in those HD patients who experience chills.

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