Relationship of Neutrophil Lymphocyte Ratio (NLR) with Parathyroid Hormone (PTH) in Maintenance Hemodialysis Patients

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Background: Neutrophil-Lymphocyte-Ratio (NLR), a simple derived parameter of routine Complete Blood Counts (CBC), has been shown to be better than WBC count as a marker for inflammation in many contexts. Inflammation is associated with adverse outcomes in hemodialysis patients. **Methods:** A cross sectional study was designed on 100 maintenance hemodialysis Patients in a tertiary care hospital in Eastern India after IRB permission and informed consent. 88 complete results became available. Complete blood count (CBC), routine PTH and biochemistry analysis were performed. KDIGO 2009 cut offs were used to classify patients by PTH levels (PTH<2ULN, PTH 2-9ULN & PTH>9 ULN). NLR was calculated and NLR of 3.5 was used as high inflammation cut off. **Results:** In Analysis of 88 samples, significant Pearson Correlation with NLR was shown by Albumin, Hemoglobin, PTH, Gender, Age, and Sugar, but involved collinearities. Multiple Linear Regression with Robust estimation of Standard Errors retained only PTH as a significant predictor (Beta= -0.273, P=0.033) of NLR and Albumin as a borderline significant predictor (Beta= -0.501, P= 0.061). The population was partitioned into 3 sets based on PTH as per KDIGO guideline. **Conclusion:** Our study suggests that PTH is a significant predictor of inflammation as measured by NLR, independent of the other parameters, and it has an overall weak negative association with inflammation especially in the mid-range (PTH 2-9 ULN) subgroup**,** which largely corroborates with available but scant literature.

Keywords: Hemodialysis (HD), Neutrophil Lymphocyte Ratio (NLR), Parathyroid Hormone (PTH), Inflammation, Multiple Regression

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Introduction

It has been estimated that more than 9.1% of the World population (697.5 million in 2017) suffer from Chronic Kidney Disease (CKD), including 115.1 million that live in India alone [1,2]. In India 1.18 million die of CKD annually [3]. Well over 2 million people are estimated to be receiving life-saving dialysis world-wide, which is only ~10% of those who need it to survive with CKD Stage 5.[4]. Chronic inflammation is an almost inseparable companion of maintenance hemodialysis (MHD) that in turn is the primary contributor to the cardiovascular mortality risks, malnutrition and the whole spectra of morbidities related to MHD [5]. Inflammation in MHD is still partially understood and multifactorial, including exogenous surface contact activation e.g. dialysis membranes and central venous catheters; in-vivo issues generating at tissue & cell levels, e.g. oxidative stress and senescence, organ level complications e.g. fluid and sodium overload, poor perfusion & hypoxia; aggravation by immune & infectious etiologies e.g. gut dysbiosis and secondary immune maladaptations, and systemic level retention of uremic toxins that include a plethora of molecules including advanced glycation end products, calci-protein particles, indoxyl sulphate and many others [6].

Neutrophil Lymphocyte Ratio (NLR) is the ratio of the neutrophil count and the lymphocyte count in peripheral blood. It is a by-product of a Complete Blood Count (CBC) which is cheap and frequently done to assess anemia, infection or inflammation and many other conditions. NLR, though not new but relatively underused, is a readily available and inexpensive index for inflammation [7]. It is cheaper than other measures of inflammation e.g. CRP, IL6 or ferritin, since NLR has been utilized for prognostication more commonly in the field of oncology and its use in other fields has been relatively rare. It has recently reemerged as an interesting marker associated with various outcomes including all-cause and cardiovascular mortality, [7–9] Heart Failure [10]. etc. It has been shown to be a better predictor of all-cause mortality than TLC (Total Leukocyte ie WBC Count) in these patients [11]. Some studies have tried to evaluate NLR as a surrogate of hsCRP in CKD population [12] but other studies have shown it to be also independently (of hsCRP) associated with endothelial dysfunction and significantly associated with progression of CKD [13].

A study from a leading nephrology group also found that among ratios with lymphocyte in the denominator, it was the only NLR but not PLT (Platelet Lymphocyte Ratio) that provided additional benefit in predicting mortality in addition to demographics, comorbidities and albumin level [8].

CKD eventually leads to a spectrum of Mineral and Bone Diseases (CKD-MBD), including Renal Osteo-Dystrophy, which in turn range from high bone turnover secondary hyperparathyroidism (SHPT) on one extreme of PTH values to low bone turnover adynamic bone disease [14] on the other extreme. If not treated, increased bone turnover in CKD results in hyperparathyroid bone disease, while overzealous treatment with calcium, calcimimetics etc can lead to too much lowering of PTH, and can be associated with low-turnover adynamic bone disease. PTH is routinely estimated in all hemodialysis patients to monitor CKD-MBD and guide the treatment to keep the PTH in a reasonable middle range. The 2003 Kidney Disease Outcomes Quality Initiative (KDOQI) guideline which recommended PTH to be kept between 130-300pg/ml, were updated by 2009 "Kidney Disease: Improving Global Outcomes" (KDIGO) guideline which recommend keeping PTH in the range of 2-9 multiples of the upper limit of normal (ULN) of the PTH [15].

Given the high level of PTH in majority of hemodialysis population and the high occurrence of inflammation, PTH has been suspected to have positive association with inflammation in this population. However not many studies have explored relation of PTH with inflammation in the dialysis population and the very few that were published show a rather weak association that changed direction in selecting PTH based subsets, [16] or no association [17]. Studies in an entirely different population: primary hyperparathyroidism and parathyroid adenoma etc. also show inconsistent association of PTH with inflammation [18].

Relationship of PTH to inflammation after hemodialysis population based on PTH based subgroups has been explored by very few studies [16,19] which suggest that paradoxically patients with lower PTH range might be more associated with higher inflammation that patients with higher PTH values.

We decided to study NLR that has not been explored well against PTH in hemodialysis.

To the best of our knowledge, the only study that tried to perform correlation and multiple regression involving NLR & PTH in CKD is Toraman et al 2019 [20] which includes a heterogenous mix of 301 patients which includes only 65 lower severity CKD patients and specifically excluded hemodialysis.

Methods

The study was done after IRB permission and informed consent in a tertiary care hospital in Eastern India. Data of CBC on Sysmex 5-part Autoanalyser and Access2 iPTH CLIA along with routine Biochemistry on samples from 100 consenting patients under maintenance hemodialysis were collected. For Statistical Analysis R version 3.6.1, Rcmdr and SPSS 23rd Edition were used. NLR was treated as the dependent variable and PTH along with other Biochemistry or hematology parameters (Albumin, Sugar, Hemoglobin) and Age and Gender which showed significant Pearson correlation in initial analysis were tested by Multiple regression. Linear regression using ordinary least square method, with robust estimation of Std. error was applied.

Results

The final analysis included data from 88 patients (64 Male & 24 Female) after excluding patients who had incomplete records.

Table 1. Demographic characteristics and laboratory parameters of all patients

Parameter	Mean±SD (N=88)
Age (Year)	51.40 ± 12.52
Gender (M, %)	73%
White blood cell (103/µL)	6.73±1.98
Neutrophil(103/µL)	4.67±1.54
Lymphocyte(103/µL)	1.46±0.55
Platelet count(103/µL)	163.25±74.06
HGB (g/dL)	9.83±1.80
NLR	3.54±1.52
Albumin (g/dL)	4.25±0.50
PTH (pg/mL)	450.45±381.17
Sugar (g/dL)	109.61±58.01

Table1: Summary of demographic characteristics and Laboratory parameters of 88 patients who had list wise complete rows of all data required for all analysis. There were 64 males and 24 Females. HGB= Hemoglobin, NLR=Neutrophil-lymphocyte ratio, PTH= Parathyroid Hormone.

Table 2. Pearson Correlationc between selected parameters

		NLR	Age	Gender	Sugar	Albumin	HGB	PTH
NLR	Pearson Correlation	1	.200	.233*	.134	-.294**	-.252*	-.231*
	Sig. (2-tailed)		.062	.029	.214	.005	.018	.031
Age	Pearson Correlation		1	.147	.137	-.346**	-.095	-.195
	Sig. (2-tailed)			.173	.203	.001	.380	.068
Gender	Pearson Correlation			1	.070	-.233*	-.061	-.095
	Sig. (2-tailed)				.518	.029	.571	.378
Sugar	Pearson Correlation				1	-.141	-.115	-.009
	Sig. (2-tailed)					.190	.285	.932
Albumin	Pearson Correlation					1	.438**	.245*
	Sig. (2-tailed)						.000	.022
HGB	Pearson Correlation						1	.105
	Sig. (2-tailed)							.330
PTH	Pearson Correlation							1
	Sig. (2-tailed)							

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

c. List wise Complete N=88

Apparently significant Pearson Correlations with NLR were shown by Albumin, Hemoglobin, PTH and Gender, whereas Age gave a borderline P value and Sugar did not show enough significance in the final subset. However, as evident from the Pearson Correlation Matrix, the parameters had significant collinearities among themselves. Multiple Linear Regression with Robust estimation of Standard Errors was done. It showed only PTH as a significant negatively related predictor (Beta= -0.273, P=0.033) of NLR and Albumin as another borderline significant negatively related predictor (Beta= -0.501, P= 0.061). Fitting Age factors into the multiple regression fetched significant (negative) contribution of PTH in NLR, but Age itself has positive but insignificant correlation (Beta 0.057, P=0.425).

Table 3: Multiple Regression with Robust Std. Error Estimation

NLR	Robust					
	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
ln_PTH	-.2726076	.1256607	-2.17	0.033	-.5226329	-.0225823
Albumin	-.5012437	.2637778	-1.90	0.061	-1.026079	.0235914

Age	.0578098	.0720233	0.80	0.425	-.085494	.2011137
Age_sqr	-.0004574	.0007128	-0.64	0.523	-.0018756	.0009609
Gender	.5659255	.3717526	1.52	0.132	-.1737456	1.305597
Sugar	.0018746	.0025078	0.75	0.457	-.0031152	.0068644
_cons	4.903606	2.472733	1.98	0.051	-.0163559	9.823568

Table 3: Dependent variable = NLR (Neutrophil Lymphocyte Ratio). Independent Variables in the final regression model were ln_PTH (natural logarithm of PTH), Albumin, Age, Gender and Sugar. Multiple regression using ordinary least square method, with robust estimation of Standard Error, was applied: N=88, F(4, 83) = 4.84, Prob > F= 0.0015, R2= 0.1644, Root Mean Square Error: 1.4282. After regression only ln_PTH was retained with significant P and Albumin was of borderline significance, and other parameters were not statistically significant.

The population was partitioned into 3 sets based on PTH as per KDIGO guideline. There were 28 Samples with PTH <2ULN, 42 samples with PTH 2-9 ULN, and 18 samples with PTH>9ULN. The negative correlation of the NLR with PTH was corroborated by the Kruskal Wallis H test across the 3 groups which showed significant difference between the group means ($\chi2=6.137$, df=2, P=0.046). Partitioning NLR by cut off of NLR>3.5 as high inflammation also fetched a significant Pearson Chi-Square test across the 3 KDIGO PTH groups (P=0.037).

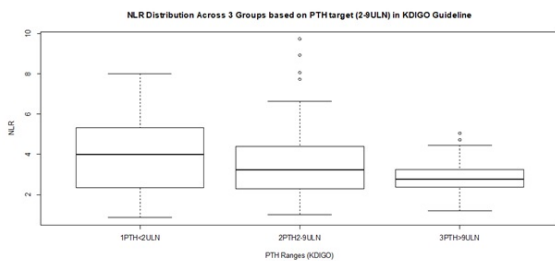Fig. 1. Distribution of NLR Across 3 groups based on PTH target in KDIGO 2009 Guideline

Fig.1: Boxplot output of Rcmdr depicting distribution of NLR Across 3 groups based on PTH target in KDIGO 2009 Guideline. Interquartile range shown as standard box with Median as bold line. Whiskers depicting range after excluding outliers depicted as small circles. Group 1 is PTH below the KDIGO target, Group 2 is within optimal PTH target as per KDIGO and Group 3 is PTH above KDIGO target.

The clear negative correlation of PTH with NLR is apparent in the Box plot. The progressively higher PTH groups have progressively lower mean NLR and also progressively narrower spread of NLR.

The Low PTH group has a higher risk of adynamic bone disorder risk. Whether the higher NLR has any connection with that risk would be worth exploring.

One-way ANOVA of the factor other than PTH (Age, Albumin, Gender, Hemoglobin, Sugar) across the three PTH based KDIGO groups in this sample set did not show significant difference between the group means. One-way ANOVA for Albumin was of borderline significance (P=0.05). While all other parameters did not show significant difference of the 3 group means by Robust ANOVA methods (Welch and Brown-Forsythe) Albumin showed significance (Welch 0.019 and Brown-Forsythe 0.043).

Table 4. ANOVA of the parameters across the 3 groups based on KDIGO PTH targets.

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
Age	Between Groups	696.468	2	348.234	2.289	.108
	Within Groups	12932.611	85	152.148		
	Total	13629.080	87			
Gender_Numeric_M	Between Groups	.153	2	.076	.376	.688
	Within Groups	17.302	85	.204		
	Total	17.455	87			
Albumin	Between Groups	1.488	2	.744	3.106	.050
	Within Groups	20.365	85	.240		
	Total	21.853	87			
Sugar	Between Groups	760.574	2	380.287	.111	.895
	Within Groups	292024.290	85	3435.580		
	Total	292784.864	87			
HGB	Between Groups	5.260	2	2.630	.809	.448
	Within Groups	276.183	85	3.249		
	Total	281.443	87			
Neu.Lymph.Ratio	Between Groups	13.725	2	6.863	3.131	.049
	Within Groups	186.315	85	2.192		
	Total	200.040	87			
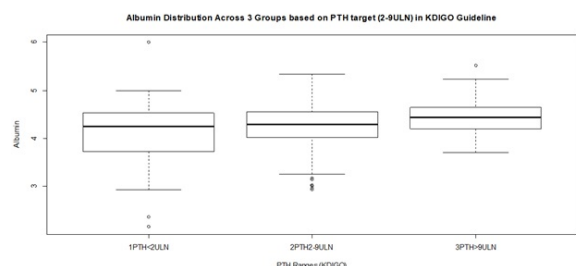
Fig 2. Albumin Distribution across 3 groups based on PTH target in KDIGO 2009 Guideline.

Fig. 2: Boxplot output of Rcmdr depicting distribution of Albumin Across 3 groups based on PTH target in KDIGO 2009 Guideline. Interquartile range shown as standard box with Median as bold line. Whiskers depicting range after excluding outliers depicted as small circles.

Discussion

In Hemodialysis there is chronic inflammation and PTH is also usually high unless treated. Paradoxically, patients of the low PTH group tend to have more inflammation (high NLR) as shown by Dukkipati et al 2010 as well as our study. Literature is very scant and rather misleading regarding association of PTH with inflammation in general. Very few articles [21,22,18] that claim to explore the relationship of PTH with inflammation in general talk about association of the low-grade inflammation in Primary Hyperparathyroidism and positive correlation with a subset of parameters which are usually weak and mutually not very consistent. A few papers show positive correlation of hsCRP with PTH in inflammatory conditions [23]. However there are also a few recent papers that have shown association of PTH with resolution of inflammation and healing in several contexts e.g. peritonitis [24] and periodontitis [25,26]. Low serum PTH level has been shown to be a predictor of infection-associated mortality in incident dialysis patients- both hemodialysis as well as peritoneal dialysis [27]. Our study explores the relationship between the inflammatory marker NLR with PTH as well as Albumin, Age, Gender and Sugar. Here, the NLR showed a weak but significant overall negative relationship to PTH.

To the best of our knowledge, there has not been many studies that have explored the nature of association of PTH with inflammation in hemodialysis patient population. Dukkipati et al 2010 [19] is the first [28] published study to show association of malnutrition-inflammation complex with low serum PTH in CKD patients. Rafieian-Kopaei et al 2012 [16] found a near-significant positive correlation of PTH with CRP in a population of 36 HD patients. They also found that when they deleted the PTH<200 their correlation became positive but statistically insignificant (r=+0.42, P=.085) but when they deleted the PTH>500 it turned significantly negative (r=-0.42, P=0.04). Our study corroborates with these findings.

Jaqueto et al 2016 [17] published data from 132 hemodialysis patients which explored relationship of PTH with inflammatory mediators IL-1, IL-6 and TNF-α, and found no association. Their analysis included Spearman Correlation (PTH as continuous variable) and Kruskal wallis test (PTH divided into tertiles with cut off at 198 and 517) but no multiple regression.

In multiple regression analysis, PTH levels in hemodialysis in our study came out as a more significant determinant of NLR as compared to Albumin, Age, Gender and Sugar. Toraman et al. 2019 [20] exploring the relationship of NLR and PTH includes a heterogenous population of 301 patients which includes only 65 CKD patients, and specifically excluded severe CKD with hemodialysis. They performed multiple regression and found only a very small contribution of PTH (β=-.001) to NLR, and a bigger contribution from Gender, Albumin, LDL and Hemoglobin. Not only is their patient population fundamentally different from our study, there is also an opposite skew in the gender distribution- 73% males in our study vs 14% Males in Toraman et al [20].

Parathyroid hormone is expected to have a deep relation with immune system [29] due to myriad reasons, including presence of PTH receptors on most immune cells including Neutrophils and lymphocytes,[30] PTH regulating action of vitamin D which is a major immune modulator, and also PTH directly regulates Calcium which is involved in most immune signaling. However, the majority of the previous research have mostly focused on one extreme where PTH is very high and there is apparently "high inflammation", but also there is an acquired immune dysfunction and the situation is majorly confounded by presence of many other uremic toxins. Whether the PTH is an aggravating factor or a compensatory factor that prevents the inflammation from further aggravation is not yet clear.

Not only does our finding of a negative correlation of PTH with NLR corroborate with Dukkipati 2010, [19] Feroze 2011,[28] Rafieian-Kopaei [16] this is also mechanistically viable. There has now been gradually emerging in-vitro (cell/organ culture) and animal data that show mutual inhibitory effects of parathyroid gland/PTH and inflammatory cells/mediators [31–34]. Neilson et al 1997 [32] showed that IL-1b suppressed PTH release from bovine parathyroid organ culture, by upregulating Calcium Sensing Receptor (CaSR) expression.

The effect was shown only in intact PTH gland ex vivo, not dissociated cells, and was neutralized by the specific inhibitor IL1Ra. CaSR the main feedback regulator of PTH secretion, is itself also directly involved in anti-inflammatory and anti-tumorigeic signaling in organs other than Parathyroid and Kidney, e.g. intestines [34].

Mouse and Rat in vivo inflammation models as early as 1991-92 [31,35] had shown that recombinant PTH agonist fragment 1-34 has direct anti-inflammatory effect tested both in paw croton oil injection and several other drug induced inflammation models, mast cell histamine release assays etc. In a recent study, McCauley et al. 2014 [33] show that injection of PTH stimulates secretion of anti-inflammatory mediators, or more specifically Specialized pro-resolving mediators (SMP) e.g. Resolvin D1 and D2, Protectin D1 etc in murine spleen and bone marrow, and synergizes in dead cell clearing activity (efferocytosis) by macrophages which is a part of inflammation resolving process. The recruitment of mesenchymal stem cells and local amplification of anti-inflammatory action by various mediators including TGF-b were also thought to be contributory phenomena. These together potentially explains the negative relationship between PTH and inflammation.

Age, Gender, Sugar etc. apparently did not seem to retain significance in this regression model. Whether all these are chance associations (or lack thereof) or due to some confounder or due to some real mechanistic causality (and its direction) cannot be concluded from the present study and needs to be replicated and discerned in further studies.

Among the 3 KDIGO based PTH subgroups, the middle subgroup i.e. the patients with optimal control of PTH had the largest numbers (48%) and showed negative correlation with NLR. However, the relationship of PTH to NLR was not uniform across subgroups. In the subgroups with suboptimal PTH (especially in the extremes), NLR seemed to have apparently positive (rather than negative) relation with PTH, none of which were statistically significant in this sample. These might need further study with greater focus on hemodialysis subsets with extreme PTH values.

The PTH measurement in hemodialysis is fraught with the accumulation of the long-lived C-terminal fragments of PTH as compared to very small proportion of the short lived bio-intact PTH.

However, the so called inactive C-terminal fragments that accumulate in hemodialysis are not truly inactive and very little is known about their mechanism of action. There is now emerging new data that show that these fragments may play complex interesting roles. Similar C terminal fragment of the related PTH related peptide also has anti-inflammatory and anti-senescence activities [36].

Conclusion

In conclusion, our study suggests that PTH is a significant predictor of inflammation independent of the other parameters.

What does the study add to the existing knowledge?

PTH has an overall weak negative association with inflammation especially in the mid-range (PTH 2-9 ULN) subgroup.

Author's contribution

Dr. Asmita Hazra: Concept, study design

Dr. Saptarshi Mandal: Manuscript preparation

Dr. Jayati Chakraborty: Manuscript preparation

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