Philippine Journal of Health Research and Development

RESEARCH ARTICLE

Prevalence and associated clinical factors of GERD (Gastro-esophageal Reflux Disease) in Filipino hemodialysis patients: A Cross-sectional study

Kento Takahashi

Author's email address: doc.kento@gmail.com

Department of Internal Medicine, Central Luzon Doctors' Hospital, Tarlac City, Philippines

ABSTRACT

Objectives: This study aimed to determine the prevalence of gastro-esophageal reflux disease (GERD) in Filipino patients on maintenance hemodialysis (HD) and investigate the demographic, clinical, and renal profiles of HD patients with and without GERD.

Methodology: This was a cross-sectional, multicenter study using a validated GERD questionnaire (GERDQ) with a Filipino translation. Patients above 18 years-old undergoing hemodialysis as outpatients were included. A GERDQ score of ≥8 was regarded as having GERD. Logistic regression analysis was conducted using variables that exhibited a significant correlation coefficient on two group comparisons as factors, with the presence or absence of GERD as the dependent variable.

Results: Included in our analysis were 264 patients, from which 36 had a GERDQ score of ≥8 (13.64% 95%CI 9.98-18.35). Factors associated with having a score of ≥8 include the following: (1) having CHD (COR 4.041, 95%CI 1.89-8.64, p<0.001), (2) being on insulin (COR 2.599, 95%CI 1.25-5.42, p=0.011), (3) anemia (COR 4.508, 95%CI 1.91-10.64, p=0.001), (4) diagnosis of both HTNKD and DKD (COR 3.853, 95%CI 1.15-12.96, p=0.029), (5) previous diagnosis of GERD (COR 6.655, 95%CI 3.18-13.91, p<0.001), (6) previous intake of antacids (COR 2.622, 95%CI 1.17-5.89, p=0.020), (7) those employed (COR 2.332, 95%CI 1.15-4.75, p=0.020), (8) alcohol consumption (COR 2.477, 95%CI 1.23-5.01, p=0.012), and (9) smoking (COR 2.405, 95%CI 1.19-4.86, p=0.014).

Conclusion: The prevalence of GERD in Filipino HD patients from three centers in Tarlac City was 13.64% and may be associated with several clinical factors such as heart disease, insulin use, anemia, hypertensive and diabetic kidney disease, previous diagnosis of GERD, use of antacids, with employment, smoking, and alcohol use. A comprehensive understanding of the relationship among these clinical factors awaits further studies in a larger number of patients.

Keywords: *prevalence, GERD, GERDQ, Filipino, chronic kidney disease, hemodialysis*

Introduction

Chronic kidney disease patients commonly experience gastrointestinal symptoms, but there seems to be a disconnect between patient perceptions and clinical definitions of normal or abnormal gastrointestinal health [1]. The prevalence of GI symptoms, including gastroesophageal reflux, causes significant impairment in activities of daily life and, when present in patients, can further lower the quality of life [2-4]. One of the most common GI symptoms in dialysis patients is reflux [5], but the association between gastro-esophageal reflux disease (GERD) and end-stage renal disease remains unclear [6]. Kawaguchi *et al.* concluded that the prevalence of GERD is increased in chronic renal failure patients using endoscopic evaluation, which was especially noted in HD patients although the risk factors were not clear [7]. It has been reported that in HD patients suffering from GERD, there is a positive correlation between the duration of dialysis, severity of renal failure, diabetes mellitus, smoking, and body mass index and a negative correlation between dialysis modalities, age, gender, use of NSAID and hypoalbuminemia [8], although these need further evaluation.

Furthermore, CKD coexists with many other comorbidities, particularly heart disease, and hence entails polypharmacy in many instances. In these patients, identifying and controlling

symptoms of GERD is important to ensure compliance with their oral maintenance medications and to differentiate this from atypical angina that is frequent in this patient population without the need for specialist referral [9]. In spite of this, upper endoscopy is generally not required for the diagnosis of GERD, especially when symptoms are typical and responding to therapy [10]. Latest guidelines then suggest the utility of a locally validated standardized questionnaire to reinforce clinical diagnosis of GERD [11] in which a linguistic validation study with regional Filipino translation is made available by Castillo-Carandang *et al.* [12].

The gastro-esophageal reflux disease questionnaire (GERDQ) is a well-developed questionnaire derived from the DIAMOND study, which includes primary care patients with upper GI symptoms. Clinical diagnosis and questionnaire scores were compared with objective diagnostic tests for GERD such as endoscopy and 24-hour pH-monitoring, Symptom Association Probability, and Proton pump inhibitor test to develop a questionnaire with high diagnostic accuracy for GERD [13]. Questions were derived from other validated questionnaires, which have symptom-based sensitivity and specificity of 65% and 71%, respectively, and the performance of the GERDQ is similar to the diagnosis of GERD when made by a gastroenterologist at 67% and 70%, respectively [14]. A pooled analysis of cluster-randomized study concluded that primary management of GERD can actually be improved using GERDQ rather than standard treatment [15]. In addition, this symptom-based approach is non-inferior to those diagnosed with endoscopy [16].

Objectives

The objectives of this study were to determine the prevalence of GERD in Filipino patients on maintenance HD using the validated GERDQ and to investigate demographic, clinical, and renal profiles of HD patients with and without GERD.

Methodology

This was a cross-sectional, multicenter study and the subjects were from the outpatient hemodialysis units of the following tertiary hospitals: Central Luzon Doctors' Hospital, Jecsons' Medical Center, and Ramos General Hospital in Tarlac City Philippines. The survey was conducted from June to October 2021. Included were end-stage renal disease (ESRD) patients who are more than 18 years old and undergoing regular HD. Excluded were those unable to answer the questionnaire, patients with cognitive impairment, patients who did not provide consent, critically ill, and those who recently underwent abdominal surgical procedures in the last three months.

The study protocol was approved by the University of the East Ramon Magsaysay Memorial Medical Center, Inc. Research Institute for Health Sciences Ethics Review Committee (RIHS ERC Code: 0893/E/2020/121). This study was conducted in accordance with the ethical guidelines of the declaration of Helsinki.

Recruitment, interview, and informed consent were conducted and obtained by independent dedicated personnel who asked participants about their symptoms using a validated questionnaire with Filipino translation to reinforce the diagnosis of GERD.

The GERDQ scores the frequency of four symptom questions: (1) heartburn, (2) regurgitation, (3) dyspepsia, and (4) nausea; and two impact questions: (1) sleep disturbance and (2) need for over-the-counter medications during the past seven days using a 4-point scale with scores ranging from 0 to 3 (0=0 days/week; 1=1 day/week; 2=2-3 days/ week; and 3=4-7 days/week). A GERD score of 8 or more was regarded as having GERD.

Several clinical profiles were also obtained and were verified using existing medical records. Information regarding the previous diagnosis of GERD and previous intake of antacids such as proton pump inhibitors, H2 receptor antagonists, aluminum/magnesium tablets, or alginates were obtained. The presence of comorbidities such as diabetes mellitus, hypertension, chronic heart and lung diseases, cerebrovascular diseases, hematologic disorders, malignancy, and immunocompromised states and their maintenance medications including antihypertensives (ACE Inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, diuretics, vasodilators), anti-diabetic medications (insulin and oral hypoglycemic agents), antiplatelets, anticoagulants, and maintenance medications for chronic kidney disease (iron supplements, sodium bicarbonate, calcium carbonate, erythropoietin stimulating agents, and potassium binders) were also collected.

Dialysis profile which includes diagnoses, modality, duration, frequency, type of vascular access, blood and dialysate flow rate, and the years in hemodialysis were obtained from existing medical records in the hemodialysis unit and other relevant histories such as employment status, smoking, and alcohol consumption.

Description of Outcome Measures

The primary outcome of the study was the prevalence of GERD among HD patients using the GERDQ. Secondary outcomes determined the presence of GERD and its association with various factors which include demographic (sex, age, civil and employment status), clinical (comorbidities and maintenance medications, previous diagnosis of GERD, previous use of antacids, smoking, and alcohol use), and renal profiles (diagnosis and years in dialysis and hemodialysis parameters).

Sample Size Estimation

The sample size was calculated using the prevalence of GERD (13.98%) reported in a recent metanalysis in 2020 [17]. The study used a confidence interval of 95% and a margin of error of 0.05. It had a computed sample size of 185 and an actual sample size of 264 with this study implemented during the COVID pandemic.

Statistical Analysis

Descriptive statistics was used to summarize the general and clinical characteristics of the participants. Frequency and proportion were used for the categorical variables (nominal/ordinal). Shapiro-Wilk was used to check for normality of interval/ratio variables such as age, years in dialysis, duration, blood flow rate, and dialysate flow rate. All interval/ratio variables were non-normally distributed, so median and range were used to describe them. Mann-Whitney U test and Fisher's Exact/Chi-square test were used to compare the difference of median and frequency between those with GERD vs. those without GERD, respectively. Odds ratios and the corresponding 95% confidence intervals from Firth logistic regression were computed to determine the association between patient profiles associated with GERD. All valid data were included in the analysis. Missing values were neither replaced nor estimated. Null hypothesis was rejected at 0.05α-level of significance. STATA 15.0 was used for data analysis.

Results

Included in our analysis were 264 patients, from which 36 had a GERDQ score of eight or higher (13.64% [95% CI 9.98–18.35]). Overall, 56% were males, the median age was 55.5 years (youngest was 22 and oldest was 90 years old), and 74% were married (Table 1). Those with GERD were employed unlike those without GERD (61.11% vs. 39.91%, p0.019).

The clinical profile of the patients is listed in Table 2. Between those with and without GERD, patients with GERD had higher frequencies of chronic heart disease (38.89% vs 13.6%, p=0.001) and anemia (27.78% vs 7.89%, p=0.001) as comorbidity, being previously diagnosed with GERD or reflux (58.33% vs 17.11%, p<0.001), previously taking antacid (77.78% vs 56.14%, p=0.017), and being on insulin (38.89% vs 19.74%, p=0.017). There were no notable differences in terms of cases of diabetes between the two groups, while the group without GERD had more patients taking iron supplement (93.42% vs. 77.78%, p=0.006).

Based on GERDQ responses of the patients (Table 3), the majority reported no symptoms of heartburn (78.41%),

Table 1. *Demographic profile of hemodialysis patients (n=264)*

	Total (n=264)	GERD (n=36)	Without GERD (n=228)	p-value
	Frequency (%); Median (Range)			
Sex Male Female	 149 (56.44) 115 (43.56)	 21 (58.33) 15 (41.67)	 128 (56.14) 100 (43.86)	0.805*
Age, years	55.5 (22–90)	56.5 (32–73)	55 (22–90)	0.921†
Civil status Single Married Divorced Widowed	 33 (12.5) 196 (74.24) 5 (1.89) 30 (11.36)	 3 (8.33) 24 (66.67) 1 (2.78) 8 (22.22)	 30 (13.16) 172 (75.44) 4 (1.75) 22 (9.65)	0.145*
Employment Status Without With	 151 (57.2) 113 (42.8)	 14 (38.89) 22 (61.11)	 137 (60.09) 91 (39.91)	**0.019***

Statistical tests used: * Fisher's Exact/Chi-square test; † Mann-Whitney U-test

Table 2. *Clinical profile of hemodialysis patients (n=264)*

	Total (n=264)	GERD (n=36)	Without GERD (n=228)	p-value
	Frequency (%); Median (Range)			
Comorbidities				
Hypertension	198 (75)	25 (69.44)	173 (75.88)	0.412*
Diabetes Mellitus	133 (50.38)	23 (63.89)	110 (48.25)	0.106*
Chronic heart disease	45 (17.05)	14 (38.89)	31 (13.6)	0.001*
Cerebrovascular disease	34 (12.88)	5 (13.89)	29 (12.72)	0.792*
Anemia	28 (10.61)	10 (27.78)	18 (7.89)	0.001*
Chronic lung disease	9 (3.41)	2 (5.56)	7 (3.07)	0.353*
Cancer	2 (0.76)	1 (2.78)	1 (0.44)	0.255*
Gout	11 (4.17)	2 (5.56)	9 (3.95)	0.650*
Other	25 (9.47)	6 (16.67)	19 (8.33)	0.126*
Previously diagnosed with GERD	60 (22.73)	21 (58.33)	39 (17.11)	<0.001*
Previous Intake of Antacids	156 (59.09)	28 (77.78)	128 (56.14)	0.017*
Maintenance Medications				
ACE Inhibitor	1 (0.38)	0	1 (0.44)	>0.999*
Angiotensin Receptor Blocker	115 (43.56)	17 (47.22)	98 (42.98)	0.718*
Alpha Adrenergic Agonist	87 (32.95)	13 (36.11)	74 (32.46)	0.704*
Beta-Blocker	59 (22.35)	8 (22.22)	51 (22.37)	>0.999*
Calcium Channel Blocker	139 (52.65)	19 (52.78)	120 (52.63)	>0.999*
Diuretics	26 (9.85)	5 (13.89)	21 (9.21)	0.370*
Iron Supplement	241 (91.29)	28 (77.78)	213 (93.42)	0.006*
Sodium Bicarbonate	196 (74.24)	24 (66.67)	172 (75.44)	0.305*
Calcium Carbonate	188 (71.21)	26 (72.22)	162 (71.05)	>0.999*
Erythropoietin Injection	244 (92.42)	32 (88.89)	212 (92.98)	0.493*
Antiplatelet	51 (19.32)	8 (22.22)	43 (18.86)	0.651*
Anticoagulant	6 (2.27)	2 (5.56)	4 (1.75)	0.191*
Insulin	59 (22.35)	14 (38.89)	45 (19.74)	**0.017***
Oral Antidiabetic	55 (20.83)	8 (22.22)	47 (20.61)	0.827*
Nitrates	6 (2.27)	2 (5.56)	4 (1.75)	0.191*
Statin	89 (33.71)	15 (41.67)	74 (32.46)	0.343*
Related history				>0.999*
Alcohol consumption	7 (7.14)	1 (5)	6 (7.69)	
Smoking	2 (2.04)	0	2 (2.56)	
Both alcohol and smoking	89 (90.82)	19 (95)	70 (89.74)	
Diagnosis				0.160*
Congenital kidney Disease	2 (0.76)	0	2 (0.88)	
Diabetic Kidney Disease	62 (23.48)	9 (25)	53 (23.25)	
Glomerulonephritis	21 (7.95)	1 (2.78)	20 (8.77)	
Gouty nephropathy	13 (4.92)	3 (8.33)	10 (4.39)	
Hepatorenal syndrome	1 (0.38)	0	1 (0.44)	
Hypertensive Kidney Disease	125 (47.35)	14 (38.89)	111 (48.68)	
Hypertensive & Diabetic Kidney Disease	15 (5.68)	6 (16.67)	9 (3.95)	
Leptospirosis	2 (0.76)	0	2 (0.88)	
NSAID induced Nephropathy	13 (4.92)	3 (8.33)	10 (4.39)	
Polycystic Kidney Disease	8 (3.03)	0	8 (3.51)	
Post-obstructive Uropathy	2 (0.76)	0	2 (0.88)	
Years in dialysis	2 (0.1–10)	3 (0.3–10)	2 (0.1–9)	0.537†
Type of vascular access				0.783*
AV fistula	232 (87.88)	31 (86.11)	201 (88.16)	
Intrajugular	32 (12.12)	5 (13.89)	27 (11.84)	
Anticoagulation - Heparin	261 (98.86)	36 (100)	225 (98.68)	>0.999*
Frequency per week				0.053*
1	4 (1.52)	0	4 (1.75)	
2	211 (79.92)	24 (66.67)	187 (82.02)	
3	49 (18.56)	12 (33.33)	37 (16.23)	
Duration, hours	4 (2–5)	4 (2.5–4)	4 (2–5)	0.765†
Blood flow rate, ml/min	250 (150–365)	200 (150–300)	250 (150–365)	0.541†
Dialysate, ml/min	500 (300–650)	400 (300–600)	500 (300–650)	0.539†
Dialysis Modality				0.136*
Conventional	263 (99.62)	35 (97.22)	228 (100)	
Sequential	1 (0.38)	1 (2.78)	0	

Statistical tests used: * Fisher's Exact/Chi-square test; † Mann-Whitney U-test

Table 3. *GERDQ responses of hemodialysis patients (n=264)*

	0 days	1 day	2-3 days	4-7 days
	Frequency (%)			
During the past week, how many days did you have a burning feeling behind your breastbone? (heartburn)	207 (78.41)	12 (4.55)	34 (12.88)	11 (4.17)
During the past week, how many days did you have stomach contents (liquid or solid) moving upwards toward your tongue or mouth? (regurgitation)	215 (81.44)	9 (3.41)	30 (11.36)	10 (3.79)
During the past week, how many days did you have pain in the center of the stomach?	207 (78.41)	25 (9.47)	25 (9.47)	7 (2.65)
During the past week, how many days did you have nausea?	226 (85.61)	27 (10.23)	9 (3.41)	2 (0.76)
During the past week, how many days did you have difficulty getting a good night's sleep because of your heartburn or regurgitation?	238 (90.15)	18 (6.82)	8 (3.03)	0
During the past week, how many days did you take additional medication for your heartburn and/or regurgitation other than what the physician told you to take?	237 (89.77)	5 (1.89)	10 (3.79)	12 (4.55)

regurgitation (81.44%), epigastric pain (78.41%), nausea (85.61%), difficulty getting a good night's sleep (90.15%), and taking of additional medication (89.77%). For those who did report these symptoms, at most, 13% felt heartburn and 11% experienced regurgitation for 2 to 3 days, while 10% had nausea for one day.

Factors associated with having a GERDQ score of 8 and above include the following (Table 4): (1) having CHD (COR 4.041, 95% CI 1.89-8.64, p<0.001), (2) being on insulin (COR 2.599, 95%CI 1.25-5.42, p=0.011), (3) anemia (COR 4.508, 95%CI 1.91-10.64, p=0.001), (4) having a diagnosis of both HTNKD and DKD (COR 3.853, 95%CI 1.15-12.96, p=0.029), (5) previous diagnosis of GERD (COR 6.655, 95%CI 3.18 - 13.91, p<0.001), (6) previous intake of antacids (COR 2.622, 95%CI 1.17-5.89, p=0.020), (7) those employed (COR 2.332, 95%CI 1.15-4.75, p=0.020), (8) alcohol consumption (COR 2.477, 95%CI 1.23 - 5.01, p=0.012), and (9) smoking (COR 2.405, 95%CI 1.19-4.86, p=0.014).

Discussion

The pooled prevalence of GERD worldwide is 14% [17-18], similar to what was found in this study (13.64%); however, there is great geographic variability [19]. On the other hand, several studies in Asia [20], Southeast Asia [18], and the Philippines [21] reported a lower prevalence of 7.4%, hence there is almost two times the prevalence of GERD in Filipino HD patients. In a study by Kawaguchi *et al.*, the reported prevalence of GERD in hemodialysis patients was 24.2% compared to a 16.3% prevalence in the general population [22]. The findings are suggestive that ESRD in hemodialysis patients may have specific risks that predispose them to GERD.

In general, the pathophysiology of GERD primarily involves gastroesophageal junction that is poorly functioning; the antireflux barrier composed of the lower esophageal sphincter and crural diaphragm, coupled with impaired esophageal clearance and alterations in esophageal mucosal integrity [23]. Gastrin, a polypeptide hormone, has been found to decrease lower esophageal sphincter pressure and increase the transient LES relaxation [24]. Patients with impaired kidney function, especially end-stage renal disease, have elevated serum gastrin concentration which can be due to impaired degradation and reduced excretion. The basal serum gastrin concentration was inversely related to the basal, maximal, and peak acid output in CRF patients with severe impairment of renal function [25-29]. In addition, patients even on hemodialysis were found to have elevated gastrin levels [30], and the values are the same, before and after HD [31-32]. Esophageal motility disorders and delayed gastric emptying may also play a role in the development of GERD in ESRD patients owing to altered myoelectric activity, or perhaps to an increased production of gastric acid [33]. It has been demonstrated that uremic patients undergoing hemodialysis had gastric dysrhythmias during HD that eventually deteriorated after hemodialysis, although autonomic neuropathy may be a confounder [34]. The delayed gastric emptying usually occurs, especially if both parasympathetic and sympathetic neuropathies are present [35].

Table 4. *Factors associated with GERDQ > 8 among hemodialysis patients (n=264)*

	Crude Odds Ratio (95% CI)	P-value
Age	1.003 (0.98–1.03)	0.814
Sex		
Male	1.0 (Reference)	-
Female	0.922 (0.46–1.86)	0.820
With Employment	**2.332 (1.15–4.75)**	**0.020**
Comorbidities		
Hypertension	0.709 (0.33–1.52)	0.375
Diabetes Mellitus	1.867 (0.91–3.83)	0.088
Chronic heart disease	**4.041 (1.89–8.64)**	**<0.001**
Cerebrovascular disease	1.181 (0.44–3.16)	0.741
Anemia	**4.508 (1.91–10.64)**	**0.001**
Chronic lung disease	2.14 (0.49–9.36)	0.312
Cancer	6.408 (0.65–63.32)	0.112
Gout	1.674 (0.4–7.06)	0.483
Previously diagnosed with GERD	**6.655 (3.18–13.91)**	**<0.001**
Previous Intake of Antacids	**2.622 (1.17–5.89)**	**0.020**
Maintenance Medications		
ACE Inhibitor	2.078 (0.08–51.98)	0.656
Angiotensin Receptor Blocker	1.189 (0.59–2.39)	0.626
Alpha Adrenergic Agonist	1.191 (0.58–2.46)	0.636
Beta-Blocker	1.028 (0.45–2.35)	0.948
Calcium Channel Blocker	1.003 (0.5–2.01)	0.993
Diuretics	1.685 (0.61–4.62)	0.311
Iron Supplement	**0.243 (0.1–0.61)**	**0.003**
Sodium Bicarbonate	0.642 (0.3–1.35)	0.243
Calcium Carbonate	1.033 (0.48–2.23)	0.934
Erythropoietin Injection	0.561 (0.19–1.69)	0.305
Antiplatelet	1.272 (0.55–2.93)	0.572
Anticoagulant	3.615 (0.74–17.68)	0.112
Insulin	**2.599 (1.25–5.42)**	**0.011**
Oral Antidiabetic	1.140 (0.5–2.61)	0.758
Nitrates	3.615 (0.74–17.68)	0.112
Statin	1.495 (0.74–3.04)	0.266
Alcohol consumption	**2.477 (1.23–5.01)**	**0.012**
Smoking	**2.405 (1.19–4.86)**	**0.014**
Diagnosis		
Congenital kidney Disease	1.126 (0.05–25.35)	0.94
Diabetic Kidney Disease	1.0 (Reference)	-
Glomerulonephritis	0.412 (0.07–2.48)	0.333
Gouty nephropathy	1.877 (0.47–7.56)	0.375
Hepatorenal syndrome	1.877 (0.07–49.6)	0.706
Hypertensive Kidney Disease	0.732 (0.3–1.77)	0.488
Hypertensive & Diabetic Kidney Disease	**3.853 (1.15–12.96)**	0.029
Leptospirosis	1.126 (0.05–25.35)	**0.94**
NSAID induced Nephropathy	1.877 (0.47–7.56)	0.375
Polycystic Kidney Disease	0.331 (0.02–6.23)	0.461
Post-obstructive Uropathy	1.126 (0.05–25.35)	0.94
Years in dialysis	1.079 (0.91–1.27)	0.366
Type of vascular access		
AV fistula	1.0 (Reference)	-
Intrajugular	1.279 (0.48–3.44)	0.626
Heparin Use	1.133 (0.06–22.39)	0.935
Frequency per week		
1	1.0 (Reference)	-
2	1.176 (0.06–22.51)	0.914
3	3 (0.15–59.72)	0.472
Duration, hours	0.765 (0.27–2.17)	0.615
Blood flow rate, ml/min	0.998 (0.99–1.01)	0.622
Dialysate, ml/min	0.999 (0.99–1)	0.597
Dialysis Modality		
Conventional	1.0 (Reference)	-
Sequential	19.31 (0.77–483.33)	0.072

Statistical test used: Firth logistic regression

Heartburn and acid regurgitation are the classic symptoms of GERD where patients generally report a burning feeling in the retrosternal area, raising into the chest and radiating toward the neck, throat, and occasionally the back [36] which is consistent in this study wherethose who reported symptoms of GERD had the most reported heartburn and regurgitation.

GERD is complex and is associated with various factors [37], and the relationship between chronic kidney disease and cardiovascular disease remains complex [38]. Along with it, this study found out that having CHD as a comorbidity in HD patients was four times more likely to have GERD, which is consistent in other observational studies noting about twice more in patients with CHD than in the general population. One plausible explanation is the adverse effect of drugs used in cardiac diseases such as Aspirin; however, no statistical significance was noted in this study. Potential explanations include esophageal-cardiac reflex, autonomic nervous systems disturbances, and visceral pain perception threshold [18,39].

Another factor associated with having a GERDQ score of at least eight in HD patients was being on insulin therapy, although there was no statistical difference with having type 2 diabetes mellitus itself. Ironically, some studies were able to determine an association between GERD and type 2 diabetes mellitus [40,41]. The variation may be due to the duration and severity of diabetes mellitus in chronic kidney disease on HD, wherein the duration and quality of diabetes control may have influenced the incidence of GERD [42], which was found to be inversely related to glycemic control [43]. The difference in findings may also be related to the limitation of the sample size and data collected, hence needs to be verified.

GERD patients with greater initial symptoms are more likely to have recurrence. In a study done in Taiwan, the recurrence rate was 30.4% [44], and it was found that patients who have a GERDQ score of more than 8 had a significantly higher incidence of recurrence which could independently predict recurrence within one year of follow-up. In relation to this study, 21 of 60 patients were previously diagnosed and treated with GERD, implicating a 35% recurrence rate, currently have a GERD score of 8 and above. And this subset of patients comprised 58% of the current GERD-positive group. Furthermore, this study found that having a GERDQ score of eight and above in hemodialysis patients, previous diagnosis of GERD is six times more likely, and previous intake of antacids such as proton pump inhibitors was about three times. Although Proton pump inhibitors are effective in the management of GERD, many patients relapse after discontinuation [45,46]. Additionally, several studies have demonstrated that up to 26-48% of GERD patients had a recurrence after 4-8 weeks of Proton pump inhibitor therapy [47,48] which is even significantly higher in our hemodialysis patients, wherein 77% of patients previously took in medications for GERD such as PPI. However, the study did not identify the timeline of diagnosis and treatment .

Anemia in CKD is a multifactorial process due to relative EPO deficiency, uremic-induced inhibitors of erythropoiesis, shortened erythrocyte survival, and disordered iron homeostasis [49]. But then, this study showed about five times more likely in GERD compared to non-GERD group. On the other side, anemia has also been associated as an alarm symptom for GERD requiring further workup to rule out ongoing blood loss attributed to an active malignancy, but of limited value [50-51]. In lieu of these, a patient currently taking an iron supplement was found to be 76% (COR 0.243, 95%CI 0.1-0.61, p-0.0030) less likely to have a GERDQ score of 8 and above (Table 4). Meta-analysis confirms that iron supplementation is also associated with significant GI-specific side effects which include abdominal pain and heartburn, although is not dose-dependent and did not specifically mention GERD [52]. This may then be a counterintuitive finding, and there may be reverse causality; such that those who have had GERD symptoms previously have already withheld iron supplements before the survey. Furthermore, in a separate study, the use of PPI and iron deficiency, a significant association was present among both persons with and without GERD [53]. Although, the inconsistencies from other studies may have been influenced by recall errors or even the difference in study population.

Interestingly, several social factors were also related to the GERD group. Among these subsets of patients, being employed while undergoing hemodialysis was higher. Patients with GERD were found to have high occupational stress scores and low quality of life [54], and it was found that the parameter having the most significant negative impact on the QoL of hemodialysis patients was an impeded possibility to continue work or studies and a change of life plans [55]. Smoking and alcohol consumption were also independently associated with increased prevalence of GERDQ score of eight or more and are consistent with a recent meta-analysis of 102 articles [18].

In this study, no statistical difference was found on the hemodialysis profile of patients such as modality, duration, frequency, type of vascular access, blood and dialysate flow rate, and years in hemodialysis. In comparison, a positive

correlation between the duration of dialysis and a negative correlation between dialysis modalities towards GERD was reported in another study [11]. The nonsignificant finding may allude to different factors as only hemodialysis as a modality was included in this study.

The study has several limitations; firstly, the study participants were drawn only from those patients seen in a single locality, and that only three dialysis centers were included for analysis, therefore the data gathered here were underestimates of the true prevalence of GERD in Filipino hemodialysis patients. Secondly, patients may have had recall errors, especially regarding their previous diagnosis of GERD. Moreover, these dialysis patients have multiple comorbidities and are on polypharmacy; hence may have missed out on some of the relevant details.

Third, the prevalence of GERD in HD may be further evaluated using other diagnostic modalities such as endoscopy or 24-pH monitoring [24]. Patients may also be followed up after treatment of GERD to verify the diagnosis. Lastly, a cross-sectional study cannot definitely establish the association between the several factors noted and GERD even if these were significant, hence a prospective study may further examine these findings.

Conclusion

This study is an attempt to understand GERD among hemodialysis patients and determine its relation to different clinical factors. The findings in the study showed a prevalence of 13.64% and that numerous factors such as heart disease, insulin use, anemia, hypertensive and diabetic kidney disease, previous diagnosis of GERD, use of antacids, with employment, smoking, and alcohol use can affect one's predisposition to having GERD which has several implications especially in managing hemodialysis patients, as many literature cite the intricate link between the quality of life and treatment outcomes.

Therefore, the author recommends a comprehensive understanding of the relationship among these clinical factors and conduct of further studies in a larger number of patients to further understand the complex interrelationships between GERD and hemodialysis and the different variables that may affect them. Clearly, there is a necessity to allocate resources for screening and treating GERD among HD patients to improve their compliance with treatment, to achieve a more holistic approach in their management, and ultimately improve their quality of life.

Competing Interest

The author declares no conflict of interest. The author completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data Sharing

The author shares the data generated from this study which is made openly and publicly available upon publication of the article.

Funding

None

Authors' Contribution

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

Acknowledgments

The author would like to thank Dr. Angela Apostol-Alday, Dr. Mark Isaiah Co, and Dr. Alvin De Aquino for their continued guidance in completing this paper. The author also would like to thank Dr. Nina Castillo-Carandang for allowing us to utilize her tool.

References

1. Trimingham C, McDonald S, Dansie K, Jesudason S, Faull R, Clayton P, *et al.* (2018) Bowel health in chronic kidney disease: Patient perceptions differ from clinical definitions. Journal of renal care [Internet]. 44(2):65–72. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29316279
2. Hammer J, Oesterreicher C, Hammer K, Koch U, Traindl O, Kovarik J. (1998) Chronic gastrointestinalsymptoms in hemodialysis patients. Wiener Klinische Wochenschrif. 287(91): 110.
3. Kassebaum NJ, Arora M, Barber RM, Bhutta ZA, Brown J, Carter A, *et al.* (2016) Global, regional, and

national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015 . The Lancet [internet]. 388(10053): 1603– 58. Available from: https://www.thelancet.com/journals/lancet /article/ PIIS0140-6736(16)31460X/fulltext #articleInformation

4. Oliveira APB, Schmidt DB, Amatneeks TM, Santos JC dos, Cavallet LHR, Michel RB. (2016) Quality of life in hemodialysis patients and the relationship with mortality, hospitalizations and poor treatment adherence. Jornal Brasileiro de Nefrologia. 38(4).
5. Zuvela J, Trimingham C, Le Leu R, Faull R, Clayton P, Jesudason S, *et al.* (2018) Gastrointestinal symptoms in patients receiving dialysis: A systematic review. Nephrology. 23(8):718–27.
6. Cekin AH, Boyacioglu S, Gursoy M, Bilezikci B, Gur G, Akin ED, *et al.* (2002) Gastroesophageal reflux disease in chronic renal failure patients with upper GI symptoms: multivariate analysis of pathogenetic factors. The American Journal of Gastroenterology. 97(6):1352–6.
7. Kawaguchi Y, Mine T, Kawana I, Yasuzaki H, Kokuho T, Toya Y, *et al.* (2009) Gastroesophageal Reflux Disease in Chronic Renal Failure Patients: Evaluation by Endoscopic Examination. J Exp Clin Med [Internet]. 34(3):80–3. Available from: http://mj-med-u- tokai.com/pdf/340305.pdf
8. Saeed Abdul-Rahman I. (2013) The prevalence of gastroesophageal reflux disease and reflux esophagitis in dialysis patients: between facts and fiction. Italian Journal of Medicine. 7(2):118–23.
9. Levin A, Tonelli M, Bonventre J, Coresh J, Donner J-A, Fogo AB, *et al.* (2017) Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. The Lancet. 390(10105):1888–917.
10. Kahrilas PJ, Shaheen NJ, Vaezi MF. (2008) American Gastroenterological Association Institute Technical Review on the Management of Gastroesophageal Reflux Disease. Gastroenterology. 135(4):1392-1413.e5.
11. Sollano J, Romano R, Leticia Ibañez-Guzman, Antoinette M, Lontok D, De Ocampo S, *et al.* (2015) Clinical Practice Guidelines on the Diagnosis and Treatment of Gastroesophageal Reflux Disease (GERD). Philippine Journal of Internal Medicine [Internet]. 53(3). Available from http://thepafp.org/website/wp-content/uploads/2020/11/Clinical_Practice_Guidelines_on_the_Diagnosis_and_Treatment_of_Gastroesophageal _ Reflux_Disease_ GERD - 1.pdf
12. Castillo-Carandang N. (2013) Linguistic Validation of GERDQ and Its Translations to Selected Regional Languages in the Philippines. Philippine Journal of Internal Medicine. Philippine Journal of Internal Medicine. 51(2):1–13.
13. Jones R, Junghard O, Dent J, Vakil N, Halling K, Wernersson B, *et al.* (2009) Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. Alimentary Pharmacology & Therapeutics [Internet]. 30(10):1030–8. Available from: http://doi.wiley.com/10.1111/j.1365-2036.2009.04142.x
14. Dent J, Vakil N, Jones R, Bytzer P, Schöning U, Halling K, *et al.* (2010)Accuracy of the diagnosis of GORD by questionnaire, physicians and a trial of proton pump inhibitor treatment: the Diamond Study. Gut [Internet]. 59(6):714–21. Available from: https://pubmed.ncbi.nlm.nih.gov/20551454/
15. Ponce J, Garrigues V, Agréus L, Tabaglio E, Gschwantler M, Guallar E, *et al.* (2012) Structured management strategy based on the Gastro- oesophageal Reflux Disease (GERD) Questionnaire (GerdQ) vs. usual primary care for GERD: pooled analysis of five cluster-randomised European studies. International Journal of Clinical Practice. 66(9):897–905.
16. Shaheen NJ. (2012) Upper Endoscopy for Gastroesophageal Reflux Disease: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians. Annals of Internal Medicine. 157(11):808
17. Nirwan JS, Hasan SS, Babar Z-U-D, Conway BR, Ghori MU. (2020) Global Prevalence and Risk Factors of Gastro-oesophageal Reflux Disease (GORD): Systematic Review with Meta-analysis. Scientific Reports [Internet]. 10(1). https://www.nature.com/articles/s41598-020-62795-1
18. Eusebi LH, Ratnakumaran R, Yuan Y, Solaymani-Dodaran M, Bazzoli F, Ford AC. (2017) Global prevalence of, and risk factors for, gastro- oesophageal reflux symptoms: a meta-analysis. Gut. 67(3):430–40
19. Sharma P, Bhatia S, Goh L. (2018) The Rise of Acid Reflux in Asia. Sharma P, Bhatia S, Goh KL, editors. New Delhi: Springer India.
20. Goh K-L. (2011) Gastroesophageal Reflux Disease in Asia: A historical perspective and present challenges. Journal of Gastroenterology and Hepatology. 26(1):2–10

21. Sollano JD, Wong SN, Andal-Gamutan T, Chan MM, Carpio RE, Tady CS, *et al.* (2007) Erosive esophagitis in the Philippines: A comparison between two time periods. Journal of Gastroenterology and Hepatology. 22(10):1650–5
22. Kawaguchi Y, Mine T, Kawana I, Yasuzaki H, Kokuho T, Toya Y, *et al.* (2009) Gastroesophageal reflux disease in hemodialysis patients. The Tokai Journal of Experimental and Clinical Medicine [Internet]. 34(2):48–52 . Available from: https://pubmed.ncbi.nlm.nih.gov/21318998/
23. Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. (2021) ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. American Journal of Gastroenterology. 117(1)
24. Straathof JWA, Lamers CBHW, Masclee AAM. (1997) Effect of gastrin-17 on lower esophageal sphincter characteristics in man. Digestive Diseases and Sciences . 42(12):2547–51
25. Ciccotosto GD, Dawborn JK, Hardy KJ, Shulkes A. (1996) Gastrin Processing and Secretion in Patients with end-stage Renal failure. The Journal of Clinical Endocrinology & Metabolism. 81(9):3231–8
26. Kes P, Filjak K, Vizner B. (1992) The effect of degree of renal function damage on the levels of serum gastrin and gastric acid secretion. Lijecnicki Vjesnik [Internet]. 114(5-8):87–92. Available from: https://pubmed.ncbi.nlm.nih.gov/1343059/
27. Ala-Kaila K, Kekki M, Paronen I, Paakkala T. (1989) Serum Gastrin in Chronic Renal Failure: Its Relation to Acid Secretion, G - Cell Density, and Upper Gastrointestinal Findings. Scandinavian Journal of Gastroenterology . 24(8):939–48
28. Paronen I, Ala-kaila K, Rantala I, Kainulainen H, Karvonen AL. (1991) Gastric Parietal, Chief, and G-Cell Densities in Chronic Renal Failure. Scandinavian Journal of Gastroenterology. 26(7):696–700
29. Muto S, Murayama N, Asano Y, Hosoda S, Miyata M. (1985) Hypergastrinemia and Achlorhydria in Chronic Renal Failure. Nephron. 40(2):143–8
30. Gold CH, Morley JE, Viljoen M, Tim LO, de Fomseca M, Kalk WJ. (1980) Gastric Acid Secretion and Serum Gastrin Levels in Patients with Chronic Renal Failure on Regular Hemodialysis. Nephron. 25(2):92–5
31. Kim MH, Kim HS, Rim KS, Bang IS, Kim MJ, Chang R, *et al.* (1986) The Studies on the Gastrin Levels in the Patients with Renal Failure. The Korean Journal of Internal Medicine. 1(1):43–8.
32. Sirinek KR, O'Dorisio TM, Gaskill HV, Levine BA. (1984) Chronic renal failure: Effect of hemodialysis on gastrointestinal hormones. The American Journal of Surgery . 148(6):732–5
33. Fallone CA, Mayrand S. (2001) Gastroesophageal Reflux and Hyperacidity in Chronic Renal Failure. Peritoneal Dialysis International: Journal of the International Society for Peritoneal Dialysis [Internet]. 21(Suppl 3) : S295 - 299 . Available from: https://pubmed.ncbi.nlm.nih.gov/11887839/
34. Ko C-W, Chang C-S, Lien H-C. (1998) Gastric Dysrhythmia in Uremic Patients on Maintenance Hemodialysis. Scandinavian Journal of Gastroenterology. 33(10):1047–51
35. Dumitrascu DL, Barnert J, Kirschner T, Wienbeck M. (1995) Antral Emptying of Semisolid Meal Measured by real- time Ultrasonography in Chronic Renal Failure. Digestive Diseases and Sciences. 40(3):636–44
36. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. (2006) The Montreal Definition and Classification of Gastroesophageal Reflux Disease: A Global Evidence-Based Consensus. The American Journal of Gastroenterology. 101(8):1900–20
37. Lee YY, McColl KEL. (2013) Pathophysiology of Gastroesophageal Reflux Disease. Best Practice & Research Clinical Gastroenterology. 27(3):339–51.
38. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJL, Mann JF, *et al.* (2013) Chronic Kidney Disease and Cardiovascular risk: epidemiology, mechanisms, and Prevention. The Lancet [Internet]. 382(9889):339–52. Available from : https://www.sciencedirect.com/science/article/pii/S0140673613605954
39. Pulkowski G, Majer M, Budzyński J, Swiatkowski M. (2006) Gastroesophageal Reflux Disease and Coronary Heart disease-- coexistence or interrelationship?. Polski Merkuriusz Lekarski: Organ Polskiego Towarzystw Lekarskiego [Internet]. 20(115):104–8. Available from: https://pubmed.ncbi.nlm.nih.gov/16617748/
40. S un H, Yi L, Wu P, Li Y, Luo B, Xu S. (2014) Prevalence of Gastroesophageal Reflux Disease in Type II Diabetes Mellitus. Gastroenterology Research and Practice. 1–4.
41. Horikawa A, Ishii-Nozawa R, Ohguro M, Takagi S, Ohtuji M, Yamada M, *et al.* (2009) Prevalence of GORD (gastro-oesophageal reflux disease) in Type 2 diabetes and a comparison of clinical profiles between diabetic patients with and without GORD. Diabetic Medicine. 26(3):228–33

42. Nishida T, Tsuji S, Tsujii M, Arimitsu S, Sato T, Haruna Y, *et al.* (2004) Gastroesophageal Reflux Disease Related to diabetes: Analysis of 241 Cases with Type 2 Diabetes Mellitus. Journal of Gastroenterology and Hepatology. 19(3):258–65
43. Lauffer A, Forcelini CM, Ruas LO, Madalosso CAS, Fornari F. (2011) Gastroesophageal Reflux Disease Is Inversely Related with Glycemic Control in Morbidly Obese Patients. Obesity Surgery. 21(7):864–70
44. Lei W-Y, Chang W-C, Wen S-H, Yi C-H, Liu T-T, Hung J-S, *et al.* (2019)Predicting Factors of Recurrence in Patients with Gastroesophageal Reflux disease: a Prospective follow-up Analysis. Therapeutic Advances in Gastroenterology. 12:175628481986454
45. Katz PO, Gerson LB, Vela MF. (2013) Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease. The American Journal of Gastroenterology [Internet]. 108(3):308–28.
46. Schindlbec k NE, Klauser AG, Berghammer G, Londong W, Muller-Lissner SA. (1992) Three Year Follow up of Patients with Gastrooesophageal Reflux disease. Gut. 33(8):1016–9
47. Min YW, Shin YW, Cheon GJ, Park KS, Kim HS, Sohn C-I, *et al.* (2015) Recurrence and Its Impact on the Health-related Quality of Life in Patients with Gastroesophageal Reflux Disease: a Prospective Follow-up Analysis. Journal of Neurogastroenterology and Motility. 22(1):86–93
48. Yang JH, Kang HS, Lee S-Y, Kim JH, Sung I-K, Park HS, *et al.* (2014) Recurrence of Gastroesophageal Reflux Disease Correlated with a Short dinner-to-bedtime Interval. Journal of Gastroenterology and Hepatology [Internet]. 29(4):730–5. Available from: https://pubmed.ncbi.nlm.nih.gov/24224689/
49. Babitt JL, Lin HY. (2012) Mechanisms of Anemia in CKD. Journal of the American Society of Nephrology [Internet]. 23(10):1631–4.
50. Clarrett DM, Hachem C. (2018) Gastroesophageal Reflux Disease (GERD). Missouri Medicine [Internet]. 115(3):214–8. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6140167
51. Vakil N, Moayyedi P, Fennerty MB, Talley NJ. (2006) Limited Value of Alarm Features in the Diagnosis of Upper Gastrointestinal Malignancy: Systematic Review and Meta - analysis. Gastroenterolog y. 131(2):390–401
52. Tolkien Z, Stecher L, Mander AP, Pereira DIA, Powell JJ. (2015) Ferrous Sulfate Supplementation Causes Significant Gastrointestinal Side-Effects in Adults: a Systematic Review and Meta-Analysis. Strnad P, editor. Public Library of Science [Internet]. 10(2): e0117383. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4 336293
53. Lam JR, Schneider JL, Quesenberry CP, Corley DA. (2017) Proton Pump Inhibitor and Histamine-2 Receptor Antagonist Use and Iron Deficiency. Gastroenterology. 152 (4) : 821 - 829.e1.54.
54. Jang S-H, Ryu H-S, Choi S-C, Lee S-Y.Jang S-H, Ryu H-S, Choi S-C, Lee S-Y. (2016) Psychological Factors Influence the Gastroesophageal Reflux Disease (GERD) and Their Effect on Quality of Life among Firefighters in South Korea. International Journal of Occupational and Environmental Health . 22(4):315–20
55. Dąbrowska-Bender M, Dykowska G, Żuk W, Milewska M, Anna S. (2018) The impact on quality of life of dialysis patients with renal insufficiency. Patient preference and adherence. 12:577-583.