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Original Article

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Main Outcomes of the DIYAL-TR Study: Regional Differences of Mortality and Morbidity in Chronic Hemodialysis Patients

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ABSTRACT

Objective: Variations in care at national or global level may have an impact on the prognosis of patients on chronic hemodialysis. We aimed to describe regional differences in all-cause mortality or cardiovascular morbidity in chronic hemodialysis patients in Turkey.

Methods: We enrolled 2461 patients who were initiated chronic hemodialysis in 93 centers in Turkey between January 27, 2017, and February 09, 2018. We included 2-year follow-up data of 1877 patients in this prospective study. The primary outcome, the rate of composite endpoint of all-cause mortality or cardiovascular morbidity, was compared between geographical regions. Secondary outcomes were the rates of hospitalization and infections.

Results: In total, 552 patients (29.4%) developed the primary outcome. The highest and lowest rates of primary outcome occurred in the Mediterranean (34.5%) and Southeastern (26.5%) & Central Anatolian regions (26.5%), respectively, with no significant differences across regions (P = .82). Hospitalization events were detected in 377 patients (20.1%). The highest rate of hospitalization was detected in the Black Sea region (33.8%), and the lowest (7.6%) in the Southeastern region. The regions did not differ in hospitalization rates (P = .88). Infections occurred in 11.3% (n = 212) of the patients. The highest and lowest rates of infections occurred in the Aegean (18.2%) and the Southeastern (2.9%) regions, respectively. We detected significant difference between geographic regions (P = .02).

Conclusions: Our study showed that almost 3 in every 10 chronic hemodialysis patients reached the primary endpoint of all-cause mortality/cardiovascular morbidity during the 2 years of follow-up. The occurrence of this outcome does not seem to exhibit geographical variation across the country.

Keywords: Cardiovascular morbidity, clinical nephrology, all-cause death

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INTRODUCTION

The incidence and prevalence of renal replacement therapy (RRT) for patients with end-stage renal disease (ESRD) is increasing worldwide.[1] Turkey, with a population of 83 million, has an RRT prevalence of 1008 pmp and incidence of 151 pmp as of 2019. By the end of 2019, 61 341 chronic hemodialysis patients were being treated at 886 hemodialysis (HD) units in Turkey while 3292 patients were receiving chronic peritoneal dialysis. The percentage of patients receiving HD treatment in private and chain centers in Turkey is 63.6.[2]

Despite the improvement in dialysis technology and knowledge, the annual mortality of individuals on HD remains high.[3] Probably the best available comparative data come from the Dialysis Outcomes and Practice Patterns Study (DOPPS), which uses a prospective design and attempts to harmonize data collection across several countries and continents.[4] The DOPPS reported that crude 1-year mortality rates from 1996 to 2002 were 6.6% in Japan, 15.6% in Europe, and 21.7% in the United States.[5] Dialysis patients have many comorbidities and a high symptom burden affecting their

quality of life.[6-8] Moreover, many of these problems are associated with increased mortality.[9-11]

Since 1990, the Turkish Society of Nephrology has been coordinating a national registry that collects data on patients receiving RRT. The reports are published annually and represent the unique source of information about demographic, epidemiological, and clinical features of ESRD necessitating RRT in Turkey and the status of the therapy methods and the changes in those parameters in years. The National Renal Registry is one of major most referred sources of information in determining national strategy and approaches regarding the control and treatment of ESRD.[2] Nevertheless, the data collected are not patient-based and represent the mean values of the last 3 months of the year of all patients of the registry centers as an overview, not focusing on either the patient outcomes or region-specific differences in ESRD care. In fact, there are differences in the distribution of number of HD centers and patients at the regional level in Turkey.[12] In addition, patient profiles and parameters were reported to differ between geographical regions.[13]

In Turkey, there are very limited data with regard to the regional differences in HD practice, treatment strategies, and clinical events over time. Besides, a nationwide study evaluating patient outcomes across regions is lacking. As part of the DİYAL-TR project, we previously reported clinical characteristics of HD patients in Turkey.[14] In this study, we aimed to describe regional differences in all-cause mortality or cardiovascular (CV) morbidity in chronic HD patients in Turkey.

METHODS

Study Design

This study was a multicenter, observational, prospective study to collect clinical data from ESRD patients who were on chronic HD treatment. The study was performed after being approved by the Ethics Committee of Ankara University School of Medicine on December 26, 2016 (approval no: 20-1038-16). A written informed consent was signed and obtained from each subject. After 1-year active recruitment period, the study continued until the last enrolled patient was observed for 2 years. This was a non-interventional study with no change upon clinical management of patients. The planned number of patients was 2500 which reflects nearly 4% of the incident and prevalent patient population in Turkey. The dropout rate during the 2-year follow-up was assumed to be 20% annually.

Relevant medical history, comorbidities, concomitant medications, and clinical and laboratory data were collected via completed electronic case report forms. No additional laboratory or diagnostic tests were requested other than those currently performed, as part of the patients' routine care.

Setting

The study was performed between January 27, 2017, and February 09, 2020. The first day the data were started to be collected was also the first recruitment day in the study. The last enrolled patient was allowed to be observed for 2 years to provide his/her data on February 9, 2020. The study was conducted in 93 centers of 7 geographical regions of Turkey.

Subjects

Adult patients (≥18 years old) who required chronic HD treatment with newly emerged (incident: <3 months) or ongoing indication (prevalent: ≥3 months) were recruited to the study. Exclusion criteria were as follows: patients (i) who withdrew their consent, (ii) lost to follow-up, (iii) transferred into another dialysis center not defined in the study protocol, (iv) under therapy in a study center withdrawn from the study, (v) in whom HD treatment was no longer required, (vi) who switched to peritoneal dialysis treatment, and (vii) who underwent renal transplantation after participating in the study.

Variables and Outcome Measures

Apart from regular recording of data on medications, dialysis prescriptions, resting blood pressure, weight, comorbidities, and laboratory measurements, the following parameters of clinical outcomes were recorded on each visit: (i) mortality, (ii) hospitalization and its duration, (iii) CV outcomes (new-onset acute myocardial infarction, new-onset atrial fibrillation, heart failure, revascularization procedure, stroke, peripheral arterial disease), (iv) vascular access problems, (v) diabetic foot amputation, (vi) infections, and (vii) renal transplantation.

The primary outcome measure was the rate of patients' all-cause mortality and CV morbidity in different regions of Turkey. The primary outcome was further compared in terms of incident/prevalent status, anemia, and hyperparathyroidism strata of the patients. Secondary outcome measures include (i) the rate of hospitalizations and infections in different regions; (ii) the difference in hemoglobin (Hb) levels in incident and prevalent HD patients in different regions, (iii) the difference in the proportion of patients with Hb levels at target, lower, and higher than target values over time in different regions, (iv) Hb concentrations in relation with incident/prevalent status of HD, age, and

MAIN POINTS

- Three in every 10 chronic hemodialysis (HD) patients faced a fatal or cardiovascular event during 2 years of follow-up.
- The rate of all-cause death or cardiovascular morbidity was similar in the regions and independent of the newly emerged or ongoing indication for HD treatment.
- One in every 5 patients were hospitalized for any reason, with no difference between the regions.
- While lower than expected, the rates of infection (11.3%) showed significant variations between geographical regions.
- Clinical care of anemia and hyperparathyroidism might have affected the occurrence of the primary outcome.

gender, and (v) the differences in parathormone (PTH), phosphate, calcium, and calcium–phosphate product levels and the changes of these parameters over time in different regions.

Statistical Analysis

Collected electronic health records data from study sites were exported into Microsoft Excel sheets. Raw data cleaning was performed in this program. After data cleaning, relevant study variables were transferred into SPSS for Windows 25.0 software (IBM Corp., Armonk, NY, USA), where all descriptive and further statistical analyses were performed. Analyzed data were expressed as mean ± standard deviation or median values and numbers and/or percentages, where appropriate. Categorical variables between the study groups were compared via chi-square or Fisher's exact test, whereas continuous variables were compared through *t*-test or analysis of variance. An overall 5% of type I error level was used to infer statistical significance.

RESULTS

Among 2570 patients enrolled in the study, 109 patients declined to give consent which yielded 2461 patients for baseline analysis. During the study period, further 584 patients (23.7%) were excluded from the final analysis for a number of reasons, mostly being lost to follow-up or transferred to a non-study center (n = 319) and renal transplantation (n = 219) (Figure 1). We analyzed data of 1877 patients who were followed for up to 2 years in the study. The patients were mostly male (65.7%), had a mean age of 57.1 ± 13.1 years, and participated from Marmara region (30.2%). Baseline demographic and clinical characteristics of the study population by the regions were summarized in Table 1. Medication use during the study is demonstrated in Supplementary Appendix 1.

In total, 552 patients (29.4%) developed the primary outcome of all-cause mortality or CV morbidity. The highest and lowest rates of primary outcome occurred in the Mediterranean (34.5%) and the Southeastern & Central Anatolian regions (26.5% for each), respectively. No significant differences were observed between geographic regions (*P* = .82) (Table 2). The primary outcome did not differ when stratified by the incident and prevalent condition across geographic regions. It was also similar in terms of incident or prevalent condition when analyzed within each particular region (Table 3).

A total of 530 hospitalization events were detected in 377 patients (20.1%) in the study. The patients with multiple hospitalizations constituted 5.6% of the study population. The highest rate of hospitalization was detected in the Black Sea region (33.8%), while the lowest rate (7.6%) was observed in the Southeastern region. The regions did not differ in terms of hospitalization rates (*P* = .88). Infections occurred in 11.3% (n = 212) of the patients with a total of 266 events. The highest and lowest rates of infections occurred in the Aegean (18.2%) and the Southeastern (2.9%) regions, respectively. We detected significant difference across geographic regions (*P* = .02) as shown in Table 4.

The patients with significant baseline anemia (Hb <9 g/dL) had higher rate of (36.7%) the primary outcome event than those with Hb ≥ 9 g/dL (28.8%, p=0.029), which was more pronounced in prevalent patients (41.8% vs. 28.7%, *P* = .011) but not preserved in incident cases (30.9% vs. 29.4%, *P* = .461). On the other hand, patients with PTH ≥600 pg/mL at baseline had lower rate of the primary outcome both in all (23.0%) and prevalent cases (23.1) compared to the subgroup with PTH <600 pg/mL (31.0%, *P* = .001 and 31.1%, *P* = .003; respectively; Table 5).

Post hoc analyses on these PTH categories showed higher baseline vitamin D (67.8%) and cinacalcet (37.0%) use in patients with PTH ≥ 600 pg/mL compared to those with PTH < 600 pg/mL (38.0% and 2.5%, respectively). On the other hand, the rate of hypoalbuminemia (<3.5 g/dL) at baseline was also higher in the latter (11.9%) than that in those with PTH ≥600 pg/mL (6.2%, *P* = .001).

While the mean baseline Hb level increased by 14.5% from 10.2 g/dL to 11.6 g/dL at the end of the study among the incident cases, it was almost unchanged in the prevalent cases (11.6 g/dL) as compared to baseline (11.6 g/dL). While

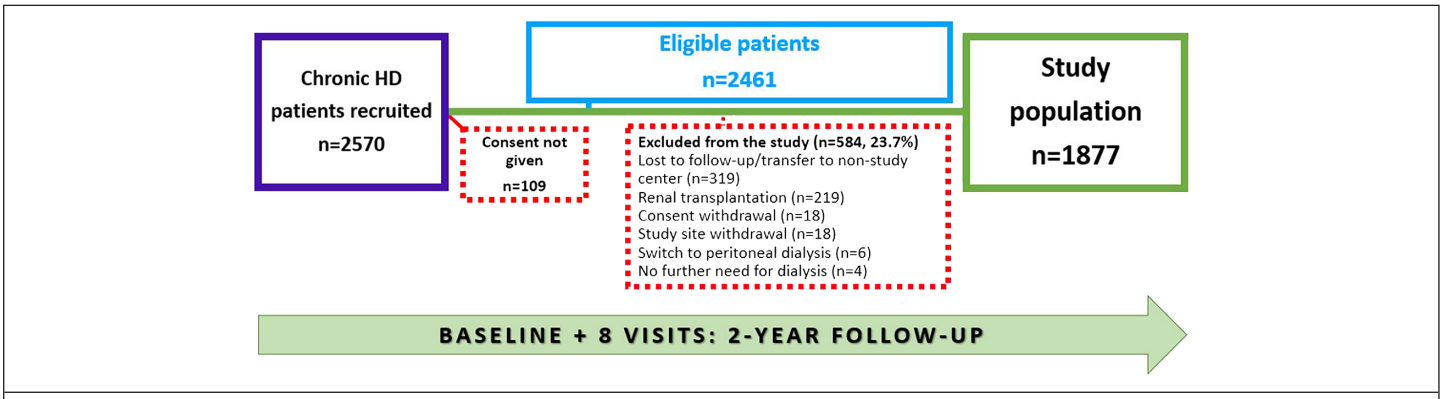

Figure 1. Flowchart of the study population from recruitment till the study end. HD, hemodialysis.

Table 1. Regional Distribution of Baseline Demographic and Clinical Characteristics of the Study Population

Characteristic	Overall	Mediterr. R.	East An. R.	Aegean R.	South E. An. R.	Central An. R.	Black Sea R.	Marmara R.
Study population, n (%)	1877 (100)	197 (10.5)	115 (6.1)	313 (16.7)	170 (9.1)	279 (14.9)	237 (12.6)	566 (30.2)
Male, n (%)	65.7	69.0	65.2	68.4	77.1	63.1	60.3	63.3
Age, mean ± SD (yrs.)	57.1 ± 13.1	56.8 ± 12.2	59 ± 13.4	58.1 ± 13.7	53.9 ± 12.7	55.9 ± 13.4	60.4 ± 11.5	57.3 ± 13.1
<45 years, n (%)	18.0	16.8	15.7	16.3	25.3	21.9	10.1	18.9
45-64 years, n (%)	51.8	59.9	42.6	51.4	57.1	50.2	50.6	50.9
≥65 years, n (%)	30.2	23.4	41.7	32.3	17.6	28.0	39.2	30.2
Body mass index (kg/m^2)	25.7 ± 4.9	25.7 ± 4.6	26.3 ± 5.1	25.4 ± 5	25.9 ± 5.1	25.8 ± 4.8	26.1 ± 5	25.6 ± 4.9
Smoking level								
Never (%)	61.8	71.5	43.5	47.9	60.0	50.0	71.2	72.0
Former (%)	18.6	10.8	20.9	23.8	21.8	26.7	11.0	16.4
Current (%)	19.6	17.7	35.7	28.3	18.2	23.3	17.8	11.6
Incident hemodialysis (%)	15.9	23.9	11.3	9.9	25.9	17.6	16.5	13.3
Any comorbidity (%)	74.7	66.5	83.5	77.6	56.5	71.3	76.8	80.6
Hypertension (%)	56.0	47.7	43.5	55.0	22.4	56.6	62.9	68.9
Diabetes mellitus (%)	29.5	31.5	33.0	31.3	35.9	26.2	33.8	24.9
Hemoglobin level								
<9 g/dL (%)	7.8	10.7	3.5	6.7	6.5	9.0	8.9	7.8
9 to <10 g/dL (%)	12.5	10.7	13.0	12.1	16.5	11.2	11.8	13.1
10 to <11 g/dL (%)	21.9	20.3	18.3	22.4	25.9	21.3	24.5	20.8
11 to <12 g/dL (%)	23.9	22.3	21.7	25.9	18.2	20.2	26.6	26.1
≥12 g/dL (%)	33.9	36.0	43.5	32.9	32.9	38.3	28.2	32.2
Transferrin level								
≤30% (%)	58.1	46.6	73.7	60.1	53.7	63.7	60.3	55.6
>30% (%)	41.9	53.4	26.3	39.9	46.3	36.3	39.7	44.4
Ferritin level								
≤500 µg/L (%)	45.0	45.5	57.0	50.8	42.1	50.7	31.6	43.0
>500 µg/L (%)	55.0	54.5	43.0	49.2	57.9	49.3	68.4	57.0
Phosphate level								
<3.5 mg/dL (%)	11.9	13.8	11.4	11.2	18.2	13.4	11.1	9.5
3.5-5.0 mg/dL (%)	55.7	51.0	49.1	56.1	60.0	55.4	51.7	59.1
>5.0 mg/dL (%)	32.3	35.2	39.5	32.7	21.8	31.2	37.2	31.4
Parathormone level								
<150 pg/mL (%)	21.6	34.6	27.2	20.1	15.3	18.7	22.8	19.7
150 to <300 pg/mL (%)	28.5	30.9	36.8	27.8	33.1	25.7	29.1	26.0
300 to <600 pg/mL (%)	29.8	27.2	23.7	32.0	29.4	30.2	28.7	31.0
≥600 pg/mL (%)	20.1	7.3	12.3	20.1	22.1	25.4	19.4	23.3
Medication use								
Antihypertensive (%)	49.0	45.9	31.3	46.3	12.4	56.8	63.7	56.1

(*Continued*)

Table 1. Regional Distribution of Baseline Demographic and Clinical Characteristics of the Study Population (*Continued*)

Characteristic	Overall	Mediterr. R.	East An. R.	Aegean R.	South E. An. R.	Central An. R.	Black Sea R.	Marmara R.
Statin (%)	9.3	6.7	3.5	14.1	3.5	9.1	14.8	8.1
ASA (%)	58.2	38.8	43.5	47.9	95.3	67.6	59.9	57.0
ESA (%)	58.3	53.8	49.6	59.1	52.9	60.4	67.5	57.8
Iron (%)	59.2	44.9	54.8	58.1	46.5	65.0	73.8	60.6
Phosphate binder (%)	80.5	71.4	60.0	81.2	70.6	86.2	86.9	85.0
Vitamin D (%)	43.4	35.7	34.8	43.1	54.7	47.6	41.4	43.4
Cinacalcet (%)	9.3	2.0%	2.6%	10.9%	7.1%	13.5%	11.4%	10.1%

SD, standard deviation; ASA, acetylsalicylic acid; ESA, erythropoiesis-stimulating agent; Mediterr. R., ; Mediterr. R.; East An. R., Eastern Anatolian Region; Aegean R., Aegean Region; South E. An. R., Southeastern Anatolian Region; Central An. R., Central Anatolian Region; R., region.

Table 2. The Rate of the Primary Outcome Across Different Regions

Geographic Region	Primary Outcome: All-Cause Death, CV Hospitalization or CV Event	
	N	%
All	552	29.4
Marmara (n = 566)	166	29.3
Aegean (n = 313)	88	28.1
Central Anatolian (n = 279)	74	26.5
Black Sea (n = 237)	80	33.8
Mediterranean (n = 190)	68	34.5
Southeastern Anatolian (n = 179)	45	26.5
Eastern Anatolian (n = 115)	31	27.0
P value*	.82	

*Chi-square test to compare the outcomes in patients across different regions. CV, cardiovascular.

the patterns in these groups were preserved in geographic strata, the highest and lowest increments from baseline were observed in the Aegean (17.8%) and Eastern Anatolian (5.8%) regions, respectively. The mean Hb levels over time usually exhibited a consistent pattern when analyzed by gender, age group, and dialysis indication except a small increment in the incident patients till visit 4 compared to baseline. Male patients had significantly higher mean Hb levels compared to their female counterparts at all time points (Figure 2A), whereas the age group did not significantly affect Hb levels (Figure 2B). The significant difference between the patients with incident versus prevalent disease regarding Hb levels was lost by visit 4 and preserved till the end of the study (Figure 2C).

The percentage of patients who were under target Hb levels (<10 g/dL) constituted 20.4% of the population at baseline and this was decreased to 13.7% at visit 8 with a relative reduction of 32.8% overall. While all regions showed varying degrees of decrease, the highest and lowest reduction in the patients who were below the targeted Hb levels were recorded in the Eastern

Table 3. The Rate of the Primary Outcome Across Different Regions Stratified by Incident or Prevalent Condition

Geographic Region	Primary Outcome: All-Cause Death, CV Hospitalization or CV Event				
	Incident		Prevalent		
	n	%	n	%	*P* value§
All	88	29.5	464	29.4	.95
Marmara (n = 566)	25	28.7	141	33.3	.41
Aegean (n = 313)	11	35.5	77	27.3	.40
Central Anatolian (n = 279)	11	26.5	63	26.5	1.00
Black Sea (n = 237)	10	25.6	70	35.4	.27
Mediterranean (n = 190)	16	34.0	52	34.7	1.00
Southeastern Anatolian (n = 179)	11	25.0	34	27.0	.84
Eastern Anatolian (n = 115)	2	15.5	29	28.4	.51
P value*	0.98		0.81		

*Chi-square test to compare the outcomes in patients across different regions within incident, or prevalent, or total category.
§Chi-square test to compare the outcomes in patients with incident versus prevalent condition within the particular region. CV, Cardiovascular.

Table 4. The Rate of the Hospitalizations and Infections Across Different Regions

	Hospitalization or Infection			
	Hospitalization		Infection	
Geographic Region	n	%	n	%
All	377	20.1	212	11.3
Marmara (n = 566)	98	17.3	49	8.7
Aegean (n = 313)	84	26.8	57	18.2
Central Anatolian (n = 279)	40	14.3	25	9.0
Black Sea (n = 237)	80	33.8	36	15.2
Mediterranean (n = 190)	28	14.2	22	11.2
Southeastern Anatolian (n = 179)	13	7.6	5	2.9
Eastern anatolian (n = 115)	34	29.6	18	15.7
P value	.88		.02	

Anatolian region by 72.7% (from 16.5% to 4.5%) and in the Marmara region by 22.6% (from 20.8% to 16.1%), respectively.

The trend of mineral bone disease parameters overall exhibited a stable pattern over the course of the study with varying degrees of differences across the regions. Compared to baseline, visit 8 showed increased levels of PTH (Figure 3A) and total calcium (Figure 3B) contrary to reduced levels of serum phosphate (Figure 3C) and total calcium–phosphate product (Figure 3D).

DISCUSSION

This multicenter prospective observational study aiming to uncover regional differences in patient outcomes receiving chronic HD treatment showed that 29.4% of the subjects developed the primary outcome of all-cause mortality or CV morbidity during the 2 years of follow-up, with no significant difference by geographic region. Among secondary objectives, hospitalization and infections occurred in 20.1% and 11.3% of the study population, where only the latter showed statistically significant variation across the regions. Indicators of anemia or mineral and bone disorders showed stable patterns, with slight improvements from baseline in newly indicated HD cases. Furthermore, routine clinical care on these parameters seems to be associated with varying effects on clinical outcomes, especially for short-term vs. long-term HD patients.

This observational study showed that almost 3 in every 10 chronic HD patients reached the primary outcome of all-cause mortality or CV morbidity in 2 years of follow-up. While exhibiting an overall decline compared to the past, the mortality rate in CKD was reported to be still high, with as high as 166 per 1000 patient-years for patients receiving HD treatment.[15] In fact, the mortality rate among incident HD patients after 2 years was reported as 33.2%,[15] which seems higher than our figures (24.5%) irrespective of its incident or prevalent status. While this might be partly attributed to the aforementioned characteristics of our population stated in the limitations, that is, less complicated cases, another contributing factor might be comparably younger mean age of our population than that reported in the literature.[16-18] In terms of the primary outcome, we did not see any geographical variation across the country. While sociodemographic indices were recently been shown to be associated with the disease burden of CKD at the global level,[1] our stratification by national regions did not distinguish such pattern or translated into varying patient outcomes. Further analyses or research focusing on sociodemographic categorization of the territories, for example, with socio-economic development index, may better help to show the impact of such stratification on patient outcomes.

The percentage of anemic HD patients under target Hb levels (<10 g/dL; 20.3%) was very similar to that reported in the nationwide renal registry (20.8%).[2] This seemed to slightly improve by a relative reduction of 32.8% at the end of 2 years. Compared to the prevalent cases who exhibited almost unchanged course of Hb levels (11.6 g/dL) throughout the study, this was especially evident in incident cases whose Hb levels reached the same level to that of prevalent cases after 12 months. The

Table 5. The Rate of Primary Outcome in Incident and Prevalent Patients by Hemoglobin and Parathormone Status

	All Patients		Incident Cases		Prevalent Cases	
Baseline Variables	No Event (%)	Event (%)	No Event (%)	Event (%)	No Event (%)	Event (%)
Hemoglobin level						
<9 g/dL (n = 147)	63.3	36.7	69.1	30.9	58.2	41.8
≥9 g/dL (n = 1728)	71.2	28.8	70.6	29.4	71.3	28.7
P	.029		.461		.011	
Parathormone level						
<600 pg/mL (n = 1470)	69.0	31.0	69.4	30.6	69.0	31.0
≥600 pg/mL (n = 370)	77.0	23.0	78.4	21.6	76.9	23.1
P	.001		.181		.003	

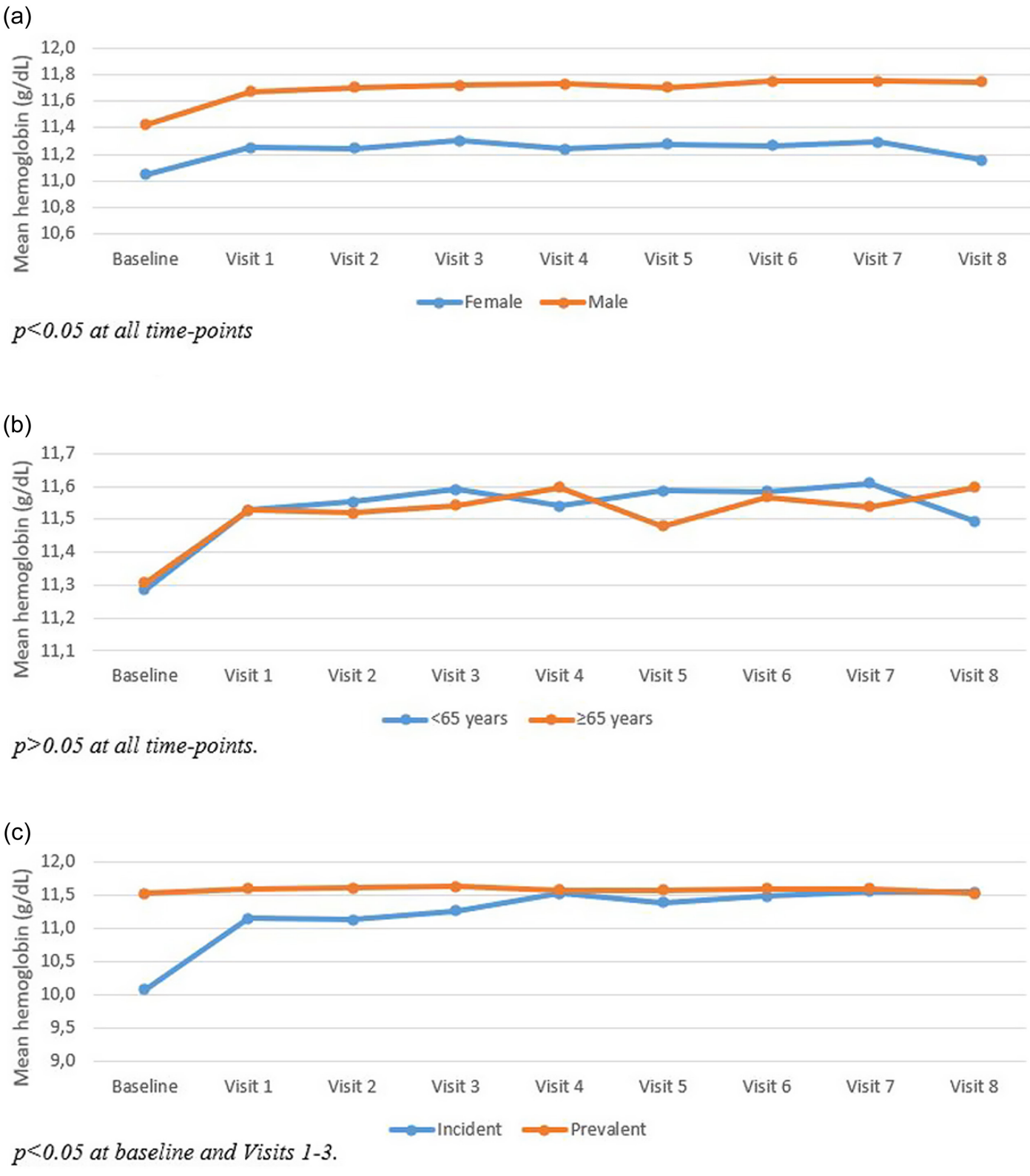

Figure 2. Hemoglobin trend by (A) gender, (B) age group, and (C) incident/prevalent disease status.

dissimilarity between incident and prevalent cases appears to be associated with differences in the rate of the primary outcome. In fact, a low Hb level is a well-recognized predictor of mortality and CV morbidity in HD patients.[19,20] In our study, those with more profound baseline anemia (<9 g/dL) among prevalent cases had a higher rate of all-cause death or CV event (41.8% vs. 28.7%). This is consistent with the findings of Japan DOPPS cohort that reported increased mortality in nonelderly

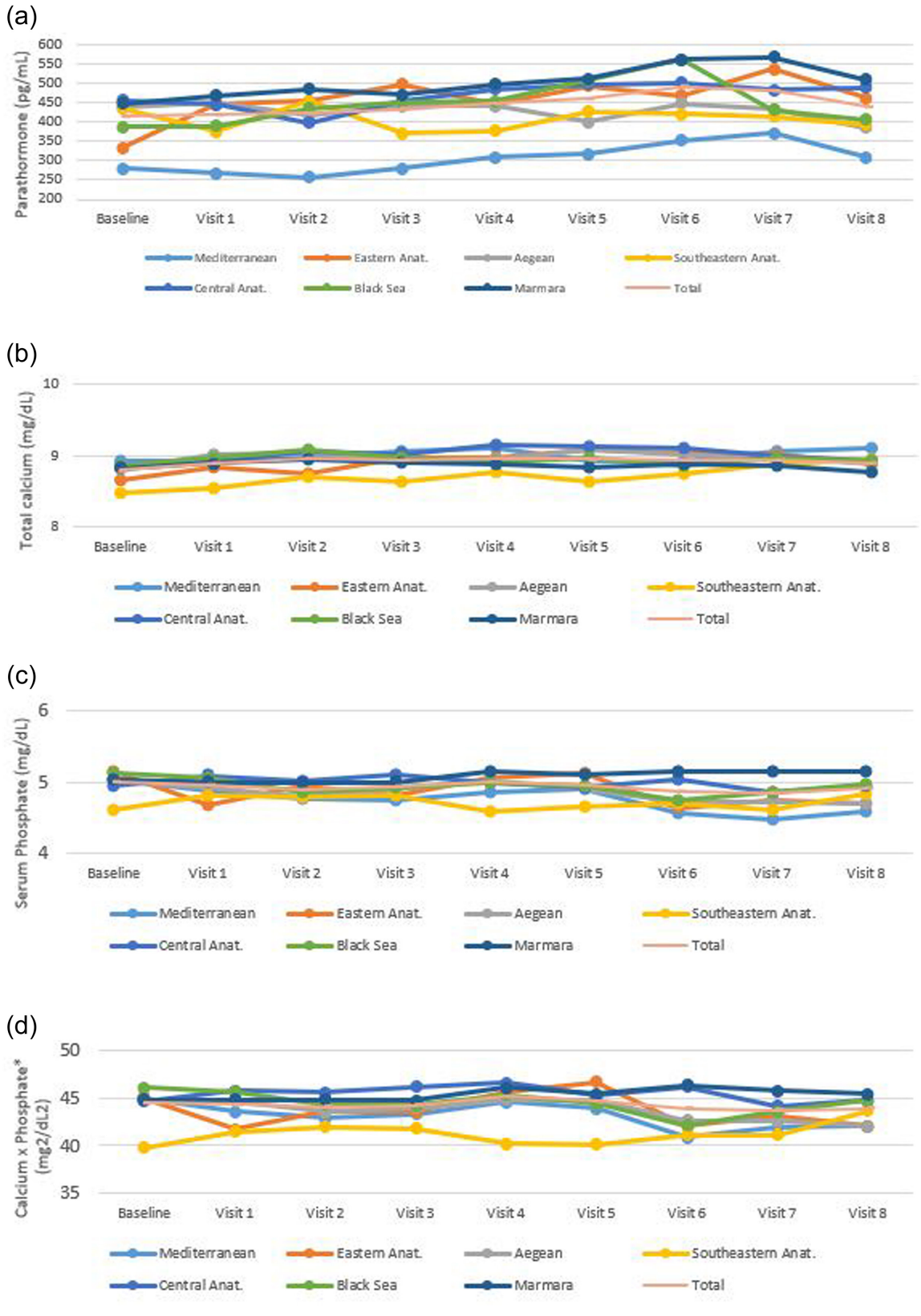

Figure 3. Regional differences in the mean serum levels of (A) parathormone, (B) total calcium, (C) phosphate, and (D) calcium × phosphate product. *Calcium level was corrected in patients with hypoalbuminemia (<3.5 g/dL).

patient strata with Hb levels <9 g/dL.[21] On the contrary, such baseline status of anemia did not affect the rate of this endpoint in incident cases. As there was no difference between incident and prevalent cases in terms of the primary outcome overall, it could be suggested that significant anemia might be associated with poorer prognosis in patients who are on long-term HD treatment. In fact, routine clinical follow-up does not seem to translate into clinical benefits for this patient group. Furthermore, modestly diminished utilization of both ESA and iron therapies during the 2 years of the study indicate that there is room for improving anemia management especially for long-term HD patients.

As a prominent feature of CKD, secondary hyperparathyroidism constitutes a critical target that should be managed to prevent and improve symptoms of mineral and bone disease or reduce vascular calcifications and mortality.[22,23] In our study, PTH and calcium levels showed mild increments compared to a slight increase in serum phosphate levels, revealing a steady pattern with minor differences across regions. Those with PTH ≥600 pg/mL at baseline formed one-fifth of the cases, which was consistent with national reports in Turkey.[2] In addition, these patients had lower rate of the primary outcome (23.0%) during 2 years of follow-up than those with PTH <600 pg/mL (31.0%). This might partly reflect better clinical care of mineral and bone disease in chronic HD patients, as supported by increased utilization of vitamin D (28% relative increment) and calcimimetic drug (63% relative increment) in our study. In fact, the figures of both vitamin D (55.5%) and calcimimetic (15.2%) were higher at the end of the study compared to those reported in Turkey (40.1% and 12.6%, respectively).[2] On the other hand, the lower event rate in our patients with hyperparathyroidism might also be partly explained by baseline hypoalbuminemia, which was less frequent (6.2%) compared to those with PTH <600 pg/mL (11.9%).

We observed that 20% of the study population were hospitalized for any reason, further a quarter with multiple hospital stays. We found no difference across regions in terms of hospitalization though the lowest rate was observed in the Southeastern Anatolian region with a rate of 7.6%. This region had also the lowest rate of infection with 2.9%. These findings might be partly attributed to comparably lower healthcare utilization in eastern regions of Turkey.[24] In addition, these regions were also reported to show the lowest antibiotic consumption in the country.[25] On the other hand, the overall infection rate (11.3%) in our study could be regarded as lower than expected since infection rates could be reported as high as 55% in HD patients followed up a median of 18 months.[26] Indeed, infection is a significant contributor to morbidity and mortality for HD patients.[27] The HEMO study showed that 23% of deaths among HD patients were attributable to infections.[28] In fact, this might explain the lower infection rates in our study as we could not identify the exact reason of death in a substantial proportion of deaths.

This study has several limitations. The study centers chosen were mostly private dialysis centers. This might introduce 2 potential biases. First, those with more comorbidities or who need to be hospitalized frequently could be more likely to receive chronic HD therapy in public hospitals. This caused more complicated cases and hence with a higher possibility of study outcomes being underrepresented in our study population. Second, the participants applying to these private centers could have different socioeconomical characteristics that may affect their access to health, thus, underestimating the observation of the rate of clinical outcomes during the 2 years of follow-up. Finally, the changing patterns of the (i) types, duration, and doses of the medications both for dialysis-related therapies and for other conditions, for example., CV drugs and (ii) laboratory parameters, for example, at least but not limited to albumin, Hb, PTH, might have affected primary and other secondary clinical outcomes of the study. As consideration of such parameters with respect to each visit could introduce a survivor bias which cannot be handled with our observational study design, we deliberately predicted primary events based on baseline parameters.

CONCLUSION

This observational study showed that almost 3 in every 10 chronic HD patients reached the primary outcome of all-cause mortality or CV morbidity in 2 years of follow-up. The occurrence of the primary outcome does not seem to exhibit geographical variation across the country. Furthermore, the association of the primary outcome with Hb and PTH levels may disclose areas for development in the clinical care of anemia as well as mineral and bone disease of chronic HD patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Ankara University School of Medicine (Approval Date: December 26, 2016; Approval Number: 20-1038-16).

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Supplementary Appendix 1. Use of Medications During the 2-Year Follow-Up

Treatment	Baseline (%)	Visit 1 (%)	Visit 2 (%)	Visit 3 (%)	Visit 4 (%)	Visit 5 (%)	Visit 6 (%)	Visit 7 (%)	Visit 8 (%)
ESA use	58.3	53.3	56.1	54.9	54.3	54.0	52.6	52.6	54.2
Type									
Epoetin alpha	34.0	32.5	32.4	31.9	26.7	26.6	25.1	28.4	28.9
Epoetin beta	0.5	0.2	0.5	0.3	0.1	0.2	0.0%	0.0%	0.0%
Epoetin zeta	16.3	13.8	14.7	13.9	15.0	13.8	14.7	14.0	10.5
Darbepoetin alpha	49.2	53.5	52.4	53.9	58.2	59.3	60.2	57.5	60.6
Route									
Subcutaneous	75.4	76.8	78.4	70.7	73.7	75.1	76.4	71.4	77.9
Intravenous	24.6	23.2	21.6	29.3	26.3	24.9	23.6	28.6	22.1
Iron use*	59.2	60.1	60.0	55.4	53.6	55.0	54.8	56.4	53.6
Vitamin D use	43.4	45.7	48.6	49.0	48.3	50.7	52.7	55.8	55.5
Route									
Oral	8.5	5.6	5.8	4.3	3.8	3.1	4.2	4.3	5.0
Intravenous	91.5	94.4	94.2	95.7	96.3	96.9	95.8	95.7	95.0
Type									
Calcitriol	47.8	49.9	50.6	51.5	46.4	46.9	46.6	45.4	45.0
Paricalcitol	52.2	50.1	49.4	48.5	53.6	53.1	53.4	54.6	55.0
Cinacalcet use	9.3	9.8	10.9	10.9	12.9	13.4	14.5	14.9	15.2
Phosphate binder use									
None	19.5	17.5	17.2	16.0	17.9	15.8	18.3	19.5	18.9
With calcium	59.9	61.8	59.6	61.5	57.4	56.7	54.6	54.8	55.4
Without calcium	20.6	20.7	23.2	22.5	24.6	27.5	27.0	25.8	25.7
L-carnitine use	26.7	25.7	25.2	26.4	21.1	18.7	17.5	17.5	15.5
Vitamin C use	13.4	11.7	11.6	14.1	11.2	10.0	9.5	10.5	7.1
Statin use	9.3	10.3	9.4	10.4	10.0	9.3	8.8	8.8	8.3
Antihypertensive use	49.0	49.1	46.9	47.5	49.7	47.5	48.1	47.4	48.9
ASA use	58.2	56.3	53.6	48.1	47.3	47.6	49.1	49.7	52.7
Type of anticoagulation									
Heparin	92.9	92.8	92.1	92.7	93.0	92.6	92.1	92.7	92.9
LMWH	7.1	7.2	7.9	7.3	7.0	7.4	7.9	7.3	7.1

ESA, erythropoiesis-stimulating agent; ASA, acetylsalicylic acid; LMWH, low-molecular-weight heparin.
*Administered by intravenous route in 97.3%-99.3% of cases.