

Chapter 7 Anemia

Hemoglobin – Iron Parameters – Erythropoietin & Iron

Anemia is a core component of ESRD pathology. During progression of chronic kidney disease prior to HD, the damage to functional kidney tissue results in the loss of most of erythropoietin (EPO) manufacturing capacity in the body. Additionally, uremic toxicity progressively induces red blood cell (RBC) fragility, causing them to break down earlier, hence reducing their half-life. Expedited breakdown of RBCs releases iron into the blood, which already suffers from major reduction in making new RBCs. Unused released iron is taken up for storage, depositing mainly in the spleen along with other organs.

Replenishment of sufficient RBCs to correct anemia requires supplementation of EPO using erythropoiesis stimulating agents (ESAs), and iron to supply free iron. Pertinent laboratory parameters have to be frequently monitored in order to optimally maintain hemoglobin (Hb) in the recommended range and judiciously supplying sufficient iron while avoiding overload.

Hemoglobin (Ref. table 7.1)

Prior to analysis, out of a total patient-months that exceeded 15,000, a handful of Hb readings < 5 g/dL or > 18 g/dL were excluded. The majority of patients in Lebanon start HD with Hb levels < 10 g/dL (Chapter 5). On maintenance HD, Hb levels in about 50% of patient-months fall in the 10–12 g/dL range, while about 1/3 continue to be < 10. Overall, mean Hb was 10.5 ± 1.6 (median = 10.5), but over a quarter of patients had Hb < 9.4 g/dL (**figure 7.1**). There were differences in mean Hb between regions with highest mean Hb in Beirut and lowest in North at 11.2 ± 1.6 and 10.1 ± 1.7 respectively (**figure 7.2**). This was reflected in the proportion of Hb patient-months below 10 g/dL which was 20% in Beirut compared to 44.7% in North. However, the difference between regions was much narrower for the 10–12 Hb range (**figure 7.2**). It appears that effort was being made to manage Hb into the 10–12 range, and outside that range, the higher proportion of values was at < 10 than at > 12 g/dL.

Figure 7.1 Distribution of Hb levels in HD patients in Lebanon by region and patient category

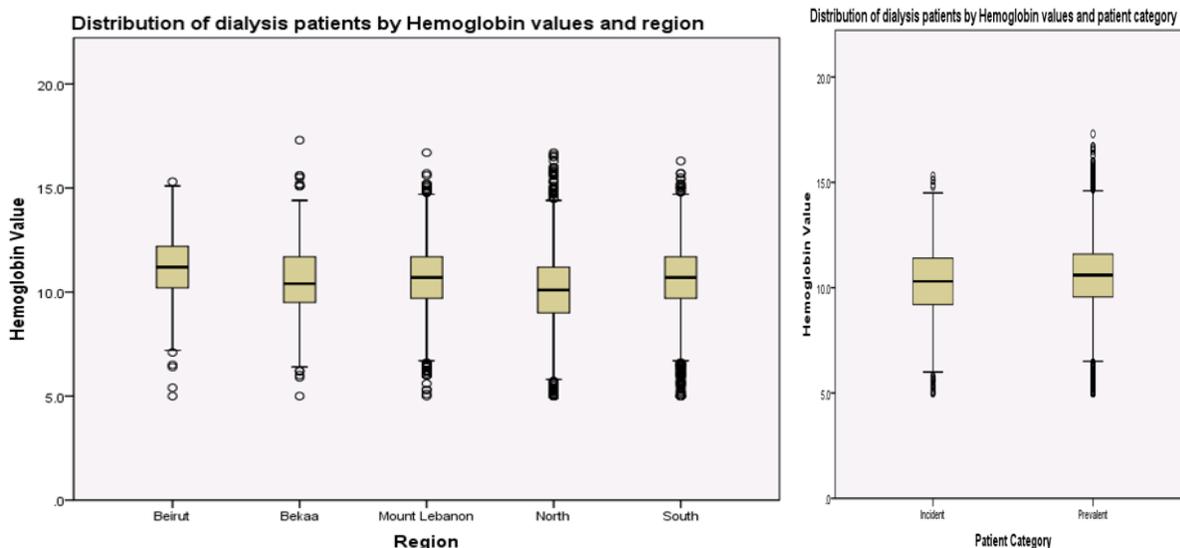
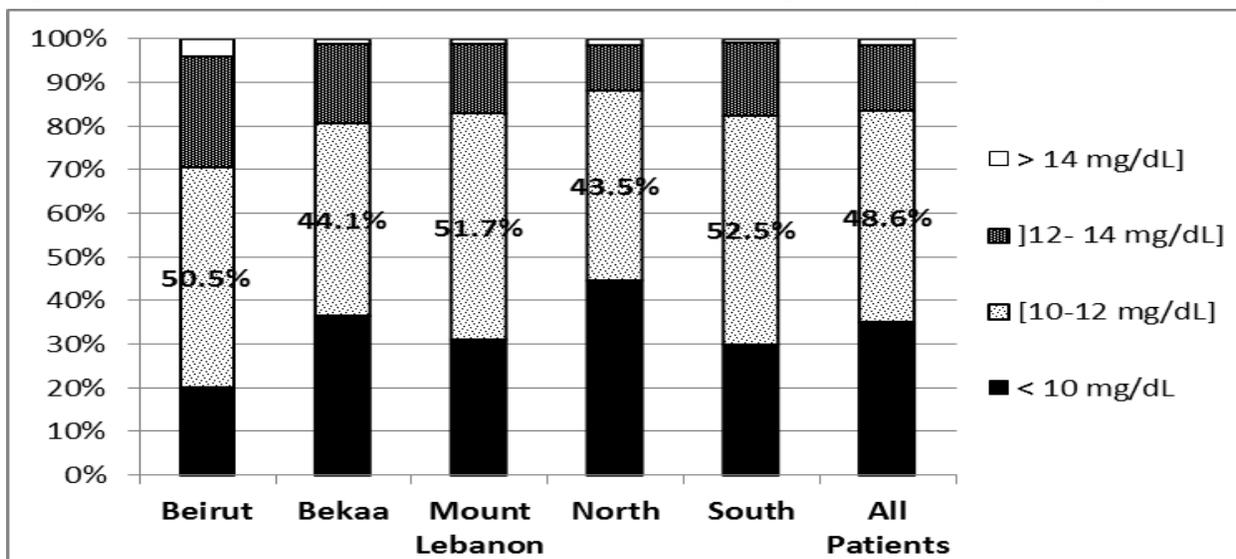


Figure 7.2 Distribution of % patient-months of Hb level ranges in HD patients by region



Iron Parameters (Ref. table 7.1)

The evaluation of iron parameters can be tricky in Lebanon as it is heavily impacted by reimbursement considerations. These parameters are measured quarterly in some patients, twice or once a year in others and none in some patients, with rather large differences by region (table 7.4). Some hospitals report all 4 iron measurements: serum iron (sFe), total iron binding capacity (TIBC), ferritin and transferrin saturation (TSAT), while others make only partial measurements. There were some differences in reporting patterns by type of coverage as shown in **table 7.5** for ferritin and sFe.

Table 7.4 Frequency (%) of testing iron parameters overall, and ferritin by region

Test Frequency	sFe	TIBC	Ferritin	Ferritin Testing by Region				
				Beirut	Bekaa	MtLeb	North	South
None	40	54.4	28.1	50.6	22.2	30.1	9.3	42.8
Once/Yr	27.8	23.2	48.1	46.5	47.5	52.3	49.2	42.3
Twice/Yr	25.1	17.5	16.8	2.3	28.4	11.5	29.3	9.3
3 or	7	5	7	0.6	1.8	6.1	12.2	5.6

Table 7.5 Frequency (%) of testing ferritin and S-Iron by type of coverage among HD patients

Test Frequency	Ferritin Testing by Coverage					Serum Iron				
	MOPH	NSSF	Army	Employee Mut.	ISF	MOPH	NSSF	Army	Employee Mut.	ISF
None	28	29.1	24.3	25	35	36.7	45.8	44.7	27.5	56.7
Once/Yr	49.8	47.1	38.2	56.3	33.3	29.5	24.1	25	26.3	28.3
Twice/Yr	16.7	14.2	27	15	21.7	26.2	24.3	21.7	36.3	15
3 or more/Yr	5.4	9.6	10.6	3.8	10	7.7	5.8	8.6	10	0

Serum Iron was generally low at deficient levels regardless of gender. Mean sFe was $49 \pm 25.2 \mu\text{g/dL}$ (median = 46) with minor differences between regions. About quarter of patients had moderate to severe low levels ($< 30 \mu\text{g/dL}$) while another quarter had levels in the normal range ($> 63 \mu\text{g/dL}$).

Total Iron Binding Capacity exhibited similar patterns to sFe. Mean TIBC was $212 \pm 59 \mu\text{g/dL}$ (median = 215), also with minor differences between regions. Lower quartile was at levels $< 182 \mu\text{g/dL}$, while upper quartile was in the normal range at levels $> 251 \mu\text{g/dL}$.

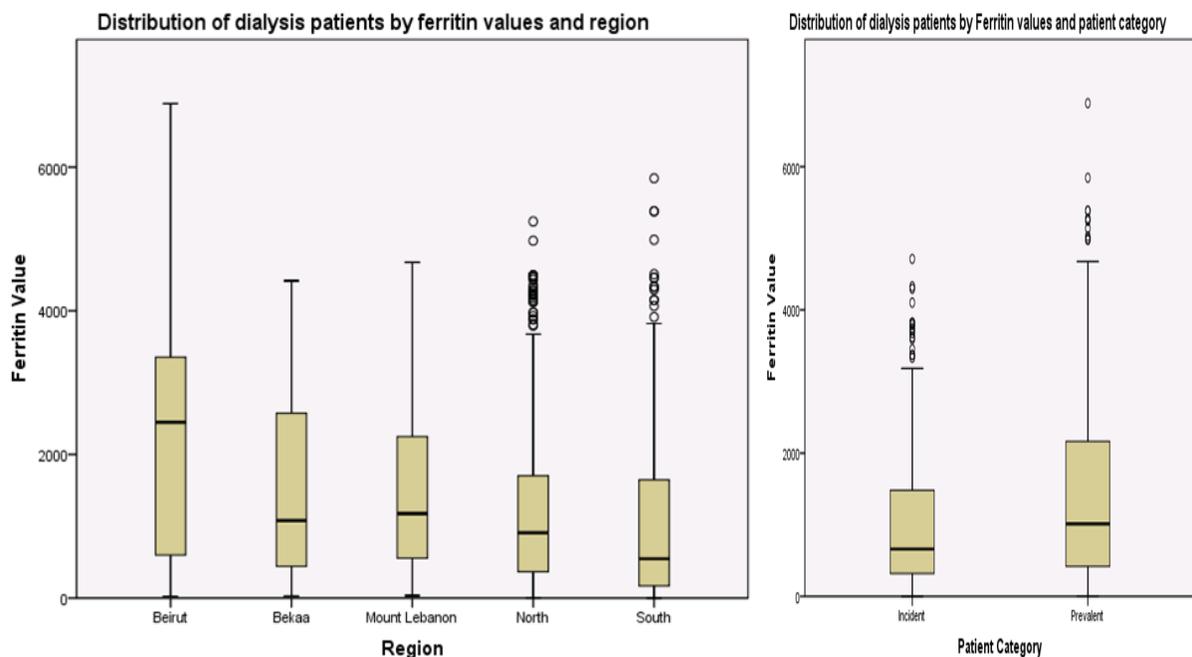
Transferrin Saturation was also generally maintained at lower end levels where mean TSAT was 24.7 ± 16.4 (median = 20). Only the upper quartile of patient-months ($> 30.8\%$) was at recommended levels. Similar to sFe and TIBC, there were minor differences between regions (**table 7.6**).

Table 7.6 Distribution of patient-months of TSAT levels among HD patients into ranges by region

TSAT (%) Range	All Patients	Beirut	Bekaa	MtLeb	North	South
≤ 20	48.6	64.5	57.6	41.8	48.8	48.6
20 - 50	45	33.1	30.3	50.6	47.4	42.6
>50	6.4	2.5	12.1	7.6	2.6	6.4

Ferritin levels were generally excessively high in HD patients in Lebanon. Mean serum ferritin was $1288 \pm 1134 \text{ ng/mL}$ (median = 922). The differential between mean and median indicates skewness due to a few patients with very high levels (**figure 7.3**). There were large differences between regions; however, mean ferritin was > 1000 in all regions! Recent starters on HD had much lower levels of ferritin (mean = 993, median = 662) compared to earlier starters (mean = 1366, median = 1170), indicating that high ferritin levels are achieved cumulatively over time during maintenance HD.

Figure 7.3 Distribution of ferritin levels in HD patients by region and patient category



Only a small proportion of patient-months (8.2%) were in deficiency levels (<100 ng/dL); yet, the proportion of patient-months in the KDOQI recommended range was less than a quarter of the measurements (**table 7.7**).

Table 7.7 Distribution of patient-months of TSAT levels among HD patients into ranges by region

Ferritin Range	All Patients	Beirut	Bekaa	MtLeb	North	South
< 100	8.2	9	6.9	2.1	8.1	17.9
100 - 500	23.2	16.7	20.2	20	24.4	27.7
501 - 800	14.7	1.3	11.6	16.7	14.2	17.3
> 800	53.9	73.1	61.3	61.2	53.3	37.1

The observation that about half the patients have TSAT levels $\leq 20\%$ while more than half the patients have ferritin levels > 800 ng/dL, suggest that it would be prudent to monitor iron parameters more frequently (quarterly) in order to rule out inflammatory processes.

Erythropoietin & Iron (Ref. tables 7.2 & 7.3)

Ongoing correction of anemia in HD patients is achieved through a delicate balance of EPO and iron supplementation. In most patients, neither is enough alone, while excesses of either of them can have precarious consequences. Their use is much impacted by reimbursement considerations: EPO is limited to \$10 per session, \$120 on average per month. IV iron is not reimbursed, but is occasionally supplied by the MOPH.

The average weekly dose of EPO was 6802 ± 3483 IU (median = 8000) Lebanon-wide and comparable averages were observed in the Bekaa, Mount Lebanon and North regions. The two exceptions were Beirut and South where the mean EPO dose was 4547 ± 3199 IU (median = 4000) and 7979 ± 3119 IU (median = 8000) respectively. There was no EPO use in a certain proportion of patient-months, probably when patients' Hb goes higher than 12 g/dL. The proportion of utilization of the 3 main EPO products is shown in **table 7.8**.

Table 7.8 Proportion of patient-months by type of EPO used by region (%)

EPO Product	All Patients	Beirut	Bekaa	MtLeb	North	South
Epotin	61.9	50.2	28.1	51.3	59.3	85.7
Eprex	12.8	15.9	31.8	27.9	6.3	2.3
Hemax	10.4	7.6	1.5	7.7	21.3	3.4
Other	3.3	3.4	1.1	2.4	6.8	1.7
None	11.6	22.9	37.5	10.7	6.3	7.9

Most ESA used (85.7%) was given to patients with Hb <10 and 10-12 g/dL (**table 7.9**). Highest doses were given to patients with Hb <10. Weekly doses were about 2000 IU lower for patients with Hb >12 g/dL.

Oral iron was used for at least one patient-month in 26.5% of patients, with wide variation between regions from a low of only 5.9% of patient-months in Beirut to a high of 53.6% of patient-months in Bekaa. However, oral iron was used in only 19.1% proportion of the total patient-months, (lowest 3.4% in Beirut and highest 30.6% in South).

Table 7.9 Proportion of patient-months of ESA use and weekly dose by hemoglobin level

Hemoglobin Level	N (Pat-mons)	Receiving ESA (%)	Proportion of Total ESA Used (%)	Mean ± SD Weekly Dose (IU)
< 10	3600	92.5	36.4	7711 ± 3729
10 - 12	5021	89.9	49.3	6456 ± 3283
>12 - 14	1379	79	13.7	5726 ± 2956
>14	58	39.9	0.6	5741 ± 2705
Overall	10,058	88.5	100	6801 ± 3481

Intravenous iron was used for at least one patient-month in 76.5% of patients, with variation between regions (low of 69.1% of patients in Mount Lebanon and high of 84.1% in North). IV iron was used in only 58.7% of total patient-months, with a low of 44.9% in Bekaa and a high of 68.4% in Mount Lebanon.

The average monthly dose of IV iron was 259 ± 200 mg (median = 200). The low patient-month utilization of IV iron in Bekaa corresponded with a high monthly dose (mean = 687 mg, median = 400 mg). The high patient-month utilization in North corresponded with a lower monthly dose (mean = 216 mg, median = 200 mg). The proportion of patients receiving IV iron was similar at levels of Hb < 14 mg/dL and dropped slightly in patients whose Hb was higher than 14 mg/dL (**table 7.10**). The frequency of ferritin testing did not seem to impact the dose of IV iron given or the levels of ferritin (**table 7.11**).

Table 7.10 Dose of IV iron by levels of hemoglobin and ferritin

(Hemoglobin measured monthly, ferritin measured mostly 1-2 times per year)

Hemoglobin Level (mg/dL)	Taking IV Iron (% of Patients)	Mean ± SD IV Iron Dose	Ferritin Level (ng/dL)	Taking IV Iron (% of Patients)	Mean ± SD IV Iron Dose
< 10	61.4%	287.4 ± 332.7	≤ 200	59.1%	281.6 ± 233.4
[10-12]	58.7%	263.2 ± 291.0	201-500	70.1%	224.7 ± 143.5
]12- 14]	54.8%	304.5 ± 470.8	501-800	68.7%	243.5 ± 169.1
> 14]	42.7%	260.6 ± 242.9	> 800	53.4%	239.7 ± 162.0
			No Measurement		284.8 ± 360.5

Table 7.11 Dose of IV iron and ferritin levels by frequency of ferritin testing

Ferritin Test Frequency	Dose of IV Iron (mg)	Ferritin Level (pg/dL)
None	248.2 ± 124.5	None
Once/Yr	250.2 ± 174.1	1005.3 ± 962.3
Twice/Yr	310.4 ± 278.7	1238.5 ± 1105.2
3 or more/Yr	236.1 ± 126.5	1286.0 ± 1138.6