Original Research Article

Etiological Spectrum of Anaemia of Elderly

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Abstract

Purpose: The elderly population has been rising in recent years all over the globe. Anemia of Elderly (AOE) or geriatric anemia in old age group is being widely observed. Independent of its cause anemia has shown to affect physical function among elderly. Various studies have shown the prevalence of anemia in elderly aged >65 years as approximately 10% which rises to 50% in individuals aged >80 years. The study was conducted with the aim to evaluate and study hematological profile and etiological spectrum of anemia in elderly. *Method:* It was a cross-sectional study conducted from November 2014 to February 2016.Elderly anemics aged 60 years and above visiting Department of Medicine, GTB hospital were evaluated and studied. *Results***:** Nutritional anemia was the most common cause of anemia in elderly. Folic acid deficiency was the most common nutritional deficiency. *Conclusions***:** Nutritonal anemia is the most common cause of anemia in elderly living in low to medium group countires while Nutritional anemia, ACD and unexplained anemia are in equal proportion in west.Folic acid reserves deplete early in elderly and their monitoring can help in predicting poor dietary intake in at risk elderly and those living in senior citizen homes.
Keywords: Anemia, Elderly, Etiology, Folate, Vitamin B12, UnexplainedAnemia, ACD.

INTRODUCTION

The elderly population has been rising in recent years all over the globe. In 2009, it constituted 11% of the world population and 7% of the Indian population. It is estimated that these figures are likely to reach up to 22% of the world and 20% of the Indian population respectively by 2050 [1].

Geriatric medicine is an upcoming field bringing along with new challenges which require significant advance planning and management. Researchers need to find solution to reduce physical and cognitive disability in older ages to help tackle the transforming demography and illnesses.Nutrition has a wide impact on health of elderly. Deficient nutrition is a well known cause of anemia which is found to increase morbidity and mortality in elderly. Abuse and neglect is also another common social problem affecting health of elderly.

Of the various non-communicable diseases in elderly, Anemia of Elderly (AOE) or geriatric anemia is being widely observed. Guidelines for the diagnosis andmanagement of anemia in older adults are lacking and this poses difficulty for clinicians. Epidemiological studies clearly link anemia with morbidityand mortality in older adults [2]. Independent of its cause anemia has shown to affect physical function among elderly. The studies have demonstrated that anemia increases risk of physical disability and is associated with impaired performance and muscle weakness. Also two independent studies found inverse gradient of risk between Haemoglobin (Hb) concentration and physical outcomes with persons having Hb concentrations 0.1-1g/dl above anemia cutoff showing significantly more decline than those with higher Hb concentrations [3].

Various studies have shown the prevalence of anemia in elderly aged >65 years as approximately 10% which rises to 50% in individuals aged >80 years [2, 4]. AOE is usually consistently mild with prevalence of severe anemia being less than 0.5% [4]. Etiologically important causes identified are anemia due to nutritional deficiencies, anemia due to inflammation and anemia due to unexplained causes (UA) [5].

The present study was done with the aim to study the haematological profile and etiological spectrum of anemia in elderly age group.

METHODS

It was a cross-sectional study conducted from November 2014 to February 2016. Sample size was calculated from previous study where the proportion of anaemia of chronic disease is around 33% in elderly subjects [2]. Taking 10% precision level on either side with 10% confidence level, sample size was calculated as 93. However, due to time and budget constraints it was limited to 75 patients. Seventy-five anemic subjects aged 60 years and above who visited medicine or geriatric department of tertiary care GTB hospital of Delhi were included in the study. Haemoglobin (Hb) cut-offs for anaemia were taken as <12 gm/dl in females and <13 gm/dl in males [6]. Those who had taken haematinics in last 10 days or received blood transfusion in last one month were excluded.

Complete clinical history and physical examination were done keeping in mind the comorbidities associated. Informed consent was taken from all the subjects prior to collection of blood samples. The study was started after we received approval from Institutional Ethics Committee for Human Research at our institute. A fasting venous blood sample was collected from the patients in Ethylene Diamine Tetraacetic Acid (EDTA) and plain iron-free vials for the following blood tests:

Complete blood counts was done with AHA LH 500 while Examination of a stained peripheral blood film (wright's stain) and reticulocyte count (Supravital staining) was done by microscopy [7]. Biochemical markers of iron status: Serum Iron (SI) [8] and Total Iron Binding Capacity (TIBC) [9] and % Transferrin Saturation (TSAT) calculated thereof. Serum Ferritin (SF), Vitamin B_{12} and Folic Acid (FA) were determined by Enzyme Linked Immunosorbent Assay (ELISA) (Calbiotech, Inc., ABNOVA and Eagle Biosciences respectively).

The criteria for diagnosis of Iron Deficiency Anemia (IDA) are SI <60 µg/dL and SF <15 µg/L [10, 11], for IDA coexisting with Anemia of Chronic Disease (ACD) was SF 15 to <30 µg/L [10], for ACD was SI <60 µg/dL, low to normal TIBC (normal - 250 to 400 µg/dL) and SF ≥ 30 µg/L[8] [10], for Vitamin B_{12} Deficiency (VB_{12}), VB_{12} levels <180 ng/L [12] and for Folic Acid (FA) deficiency, FA levels <3µg/L [11]. UA was diagnosed when patient could not be categorised in any of the above categories.

Statistical Analysis was done using SPSS software version 20. Mean, standard deviation and median were calculated for all quantitative parameters. Frequency distribution tables were prepared for all the categorical data. All quantitative data was compared using independent t-test (mean Hb levels of two age groups 60-80 years and >80 years and between men and women).P-value <0.05 was considered significant.

RESULTS

Clinical Profile

The mean age of subjects was (±SD) was 68.1 (±7.5) years and 69 (92%) were between 60-80 years while six (8%) were over 80 years. In our study, we had 45 (60%) men and 30 (40%) women. Clinical diagnosis of the anaemic subjects are shown in graph Figure-1.

Etiological Spectrum

Etiology of anemia in elderly broadly summed up under these three categories namely nutritional anemia, Anemia of chronic disease (ACD) and UA with also a case of anemia of kidney disease.

Nutritional anemia was the most common cause of AOE (37, 49.3%) (Figure-2). It was mainly found due to iron (IDA), vitamin B_{12} deficiency, folic acid (FA) deficiencies. FA deficiency was the commonest cause of nutritional anemia seen in 22 (29.3 %) cases. IDA was seen in 16 (21.3%) cases. One patient had IDA coexisting with both ACD and FA deficiency. ACD was the second most common cause of AOE seen in 36 (48%) patients. Figure 2 shows the overlap between ACD and nutritional anemia. 28% cases had isolated ACD, 29.3% cases had isolated nutritional anemia, however, overlap was seen in 20% of the cases. UA was seen in 16 (21.3%) patients. One patient was that of CKD.

There was no significant difference observed in frequency of etiologies when studied in 60-80 years and >80 years subgroup.

Hematologic Profile

Hematological profile of elderly subjects have been described in Table-1.

Difference between mean hemoglobin levels in the age groups 60-80 years and >80 years age was not found to be statistically significant (p value=0.78). Also difference in mean Hb levels between men and women was not found to be statistically significant (p value=0.62).

Mean Hb were not statistically different in all the groups when compared individually with whole sample size. However, in IDA and cases with deficiency of both Vitamin B12 and Folic acid it showed statistical difference (p value=0.04 & p =0.018 respectively). This indicates elderly with anemia having IDA or vitamin B12 and folic acid deficiency together are likely to have lower hemoglobin levels than other elderly anemic patients.

Severity of Anemia

43 (57.3%) subjects had moderate anemia followed by mild anemiain 27 (36%) and only few were severely anemic 5 (6.7%) (Table-1). Mild anemia was defined as Hb>10gm/dl, moderate anemia 6-10g/dl, severe <6g/dl. Mild anemia in elderly was largely due to either ACD or UA. Moderately anemic subjects had ACD, UA and IDA as the most common causes. While severely anaemic subjects had combined VitB12 and Folic acid deficiency as the most common cause (Table-2).

In majority of cases morphology of anemia was normocytic in 48 (64%) cases with mean MCV of 88.1 ± 5.3 fLfollowed by microcytic in 16 (21.3%) cases with mean MCV of 72.9 ± 5.6 fLand macrocytic in 11 (14.7%) cases with mean MCV of 112.6 ± 12.4 fL (Table-3).

Biochemical profile (Iron Parameters, folate and vitamin B$_{12}$ levels)

Biochemical profile of subjects is shown in Table-4. The mean SI and TSAT were low and TIBC was high for microcytic anemia as compared to macrocytic anemia. Similarly it was seen that median values of serum folate and VB$_{12}$ were low in macrocytic anemia as compared to microcytic anemia.

Study of etiologic spectrum according to the morphologic type of anemia (Table-3)
Microcytic hypochromic (MCHC) anemia (16/75)

Iron Deficiency Anemia was the most common cause (31.3%). IDA was also seen in combination with ACD (6.3%) and VB$_{12}$D and FA deficiency (6.3%). ACD existed mostly in combination with other nutritional deficiencies like IDA (6.3%), FA

deficiency (12.5%), VB$_{12}$ deficiency and FA deficiency (6.3%). There was only one case with uncomplicated ACD. It is noteworthy that two cases of with deficiencies of both vitamin B12 and folic acid had low MCV. Strangely there was one case of pure FA deficiency too. This patient had serum folate levels of 2.2µg/L with normal vitamin B$_{12}$ levels. Patient did not have hypoferremia with SI 68mg/dL, TIBC 258 µg/L, TSAT 26.3% and SF 40 ug/L. Two cases of UA 2(12.5%) had microcytic hypochromic anemia (Table-2). The mean (±SD) SI was 50.9 ± 21.6 µg/dL, mean (±SD) TIBC was 291.9 ± 102.9 µg/L, mean (±SD) TSAT was 21.8 ± 16.1 % and median SF was 26 µg/L (Table-4).

Normocytic Normochromic anemia (NCNC, 48/75)

Anemia of chronic disease was among the most common causes of NCNC anemia 20 (41.7%) and like in MCHC anemia was also present in combination with nutritional deficiencies of iron, VB$_{12}$ and FA. 12 (25%) patients of UA were the other major contributor (Table-2). The mean (±SD) SI was 58.5 ± 28.9 µg/dL, mean (±SD) TIBC was 237.6 ± 80.4 µg/L, mean (±SD) TSAT was 26.8 ± 15.2 % and median SF was 95 µg/L (Table-4).

Macrocytic anemia (11/75)

FA deficiency was seen in maximum number of cases (7 cases, 63.7%) followed by VB$_{12}$D (5 cases, 27.3%) and ACD (2 cases, 18.2%). There were two cases of UA also in this category (Table-2). The mean (±SD) SI was 79.6. ± 28.4 µg/dL, mean (±SD) TIBC was 176 ± 43.8 µg/L, mean (±SD) TSAT was 46.8 ± 16.1%, median SF was 315 µg/L, median VB$_{12}$ was182 ng/L, median FA was 2.7 µg/L (Table-4).

Table-1: Hematological profile of elderly with anemia (n=75)

Parameter	Mean ± SD	Range
Hb (g/dl)	9.2 ± 1.8	2.9 - 12.6
HCT (%)	30 ± 5.76	10 - 39.7
RBC (x 10^{12}/l)	3.5 ± 0.8	1.2 - 5.8
MCV (fl)	88.5 ± 13.6	60 - 137
MCH (pg)	27.2 ± 4.7	18 - 39.7
MCHC (g/dl)	30.5 ± 2.5	20.1 - 34.6
TLC (×10^9/l)	8.9 ± 4.6	1.9 - 31.3
Platelet count (×10^9/l)	232.9 ± 131.9	19 - 650

Hb – Hemoglobin; PCV – Packed Cell Volume; RBC – Red Blood Cell count; MCV – Mean Corpuscular Volume; TLC – Total Leucocyte Count;

Table-2: Difference in the severity of anemia due to various etiologies in elderly (N=75)

S. NO	Etiology	Hb (Mean ± SD)	Mild Anemia No. (%)	Moderate Anemia No. (%)	Severe anemia No. (%)
1.	ACD	9.5 ± 1.6	10 (37.04)	10 (23.26)	1 (20)
2.	IDA	7.9 ± 2.3	0 (0)	6 (13.95)	1 (20)
3.	IDA with ACD	9.8 ± 0.4	1 (3.7)	3 (6.98)	0 (0)
4.	VB$_{12}$D	8.9 ± 1.8	1 (3.7)	1 (2.33)	0 (0)
5.	FA deficiency	9.2 ± 1.7	1 (3.7)	4 (9.30)	0 (0)
6.	CDA	9.8 ± 2.3	2 (7.41)	2 (4.65)	0 (0)
7.	ACD with VB$_{12}$D& FA deficiency	8.5 ± 2.6	1 (3.7)	1 (2.33)	1 (20)
8.	ACD with IDA& FA deficiency	8.1	0 (0)	1 (2.33)	0 (0)
9.	UA	9.5 ± 1.7	6 (22.22)	10 (23.26)	0 (0)
10.	AKD	9.9	0 (0)	1 (2.33)	0 (0)
11.	FA deficiency and VB$_{12}$D	7.1 ± 2.8	0 (0)	2 (4.65)	2 (40)
12.	ACD with FA deficiency	10.1 ± 1.1	4 (14.81)	2 (4.65)	0 (0)
13.	ACD with VB$_{12}$D	10.8	1 (3.70)	0 (0)	0 (0)
	Total		**27 (36)**	**43 (57.3)**	**5 (6.7)**

ACD: Anemia of chronic disease, IDA: Iron deficiency anemia, FA: Folic acid, VB$_{12}$D: Vitamin B$_{12}$ deficiency, CDA: Combined deficiency anemia, AKD: Anemia of kidney disease, UA: Unexplained anemia, Hb: Hemoglobin, *P value <0.05 is considered significant.

Table-3: Causes of microcytic, normocytic and macrocytic anemia in elderly (N=75)

SNO.	ETIOLOGY	N (%)	Microcytic Anemia (n, %)	Normocytic Anemia (n, %)	Macrocytic Anemia (n, %)
1.	ACD	21 (28)	1 (6.3)	20 (41.7)	0
2.	IDA	7 (9.3)	5 (31.3)	2 (4.2)	0
3.	ACD with FA deficiency	6 (8)	2 (12.5)	2 (4.2)	2 (18.2)
4.	FA deficiency	5 (6.7)	1 (6.3)	2 (4.2)	2 (18.2)
5.	IDA coexisting with ACD	4 (5.3)	1 (6.3)	3 (6.3)	0
6.	VB$_{12}$Dand FA deficiency	4 (5.3)	0	1 (2.1)	3 (27.3)
7.	CDA	4 (5.3)	2 (12.5)	2 (4.2)	0
8.	ACD with VB$_{12}$D and FA deficiency	3 (4)	1 (6.3)	2 (4.2)	0
9.	VB$_{12}$D	2 (2.7)	0	0	2 (18.2)
10.	ACD with VB$_{12}$D	1 (1.3)	0	1 (2.1)	0
11.	ACD with IDA with FA deficiency	1 (1.3)	0	1 (2.1)	0
12.	AKD	1 (1.3)	1 (6.3)	0	0
13.	UA	16 (21.3)	2 (12.5)	12 (25)	2 (18.2)
	Total	75 (100)	16 (100)	48 (100)	11 (100)

ACD: Anemia of chronic disease, IDA: Iron deficiency anemia, FA: Folic acid, VB$_{12}$D: Vitamin B$_{12}$ deficiency, CDA: Combined deficiency anemia, AKD: Anemia of kidney disease, UA: Unexplained anemia.

Table-4: Iron, folate and vitamin B12 parameters in elderly with anemia (n=75)

Parameter	Total	Microcytic	Normocytic	Macrocytic
SI (Mean ± SD)	59.7 ± 28.4	50.9 ± 21.6	58.5 ± 28.9	79.6 ± 28.4
TIBC(Mean ± SD)	241.1 ± 87.8	291.9 ± 102.9	237.6 ± 80.4	176 ± 43.8
TSAT(Mean ± SD)	28.4 ±17.1	21.8 ± 16.1	26.8 ± 15.2	46.8 ± 16.1
SF (Median)	95	26	95	315
Vitamin B12 (Median)	453	366.50	472.5	182
Folate (Median)	4.9	5.20	5.35	2.7

TIBC – Total Iron Binding Capacity; %TSAT – Percentage Transferrin Saturation; SI- Serum Iron. Serum Ferritin (SF).

Table-5: Comparison of etiological spectrum of anemia in elderly in different studies

Etiology of anemia	Present study, Jain *et al.*, (%) N=75	Tettamani *et al.*, (%) N=493
Vitamin B$_{12}$ or Folate deficiency	14.67	10.1
- Low vitamin B$_{12}$	2.6	3.9
- Low folate	6.6	4.2
-Low vitamin B$_{12}$ + low folate	5.33	2.0
Iron deficiency anemia (IDA)	14.6	16
-IDA	9.3	9.5
-IDA + low vitamin B$_{12}$ and/or folate	5.3	6.5
Anemia of chronic disease (ACD)	48	17.4
- ACD	28	8.1
-ACD + low vitamin B$_{12}$ or folate	13.3	3.7
-ACD + IDA	5.3	2.4
-ACD + IDA and low vitamin B$_{12}$ or folate	1.3	1.4
Renal insufficiency	1.3	15
Unexplained anemia (UA)	21.3	26.4
Hemoglobinopathies	0	14.4
Other types of anemia	0	0.6
Total	**100**	**100**
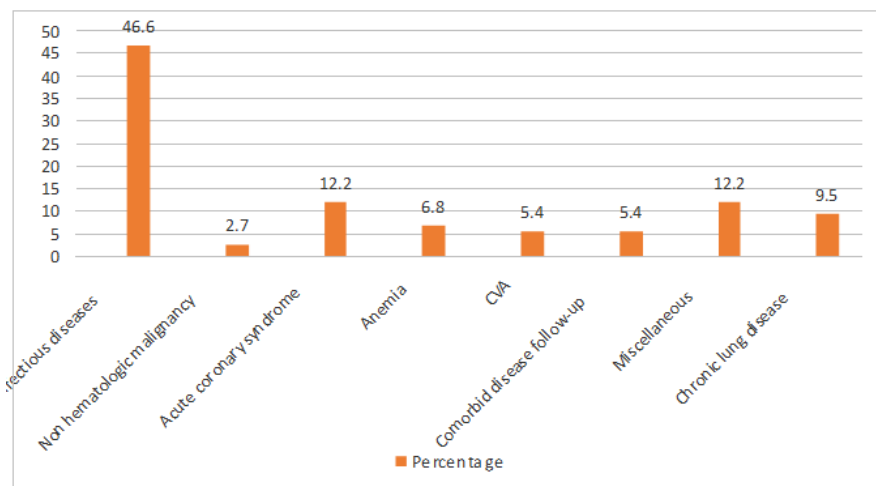
Fig-1: Clinical diagnosis of elderly with anemia (n=75)
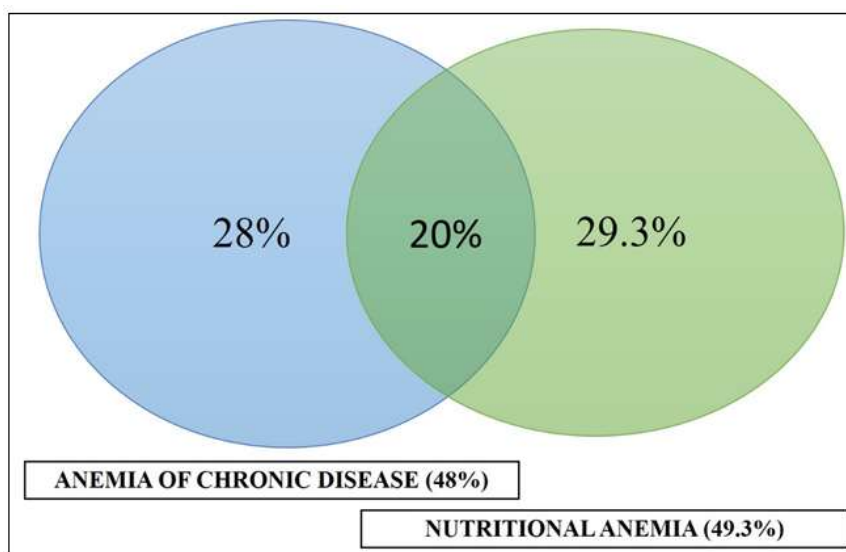
Fig-2: Overlap between Anemia of chronic disease and Nutritional anemia (N= 58)

DISCUSSION

Haematological profile and Etiology of AOE have been extensively studied in this study. NHANES III done in high income group countries revealed Nutritional anemia, ACD and Unexplained anemia were present in almost equal proportions. Etiological spectrum in elderly anemics can vary with the difference in economic status of population with nutritional anemia being more common in low to middle income group countries.

In our study nutritional anaemia was the commonest cause followed by ACD and UA.A large number of patients showed a multiple causes. FA deficiency was the most common nutritional deficiency followed by IDA.

Tettamani *et al*., conducted a prospective, population based study on prevalence, Incidence and types mild anemia in all residents 65 years and older in Biella, Italy in 2003-2008. This was a community-based study which showed the prevalence of anemia in elderly to be 14.2% [13]. There were 70.1% anemic patients between 65-80years and 29.1% above 80years of age [13].

In our study, patients aged from 60-90 years with median age of 70 years. Ours was a hospital-based study and hence prevalence of anemia could not be commented upon. Overall there were 92 % elderly anemic between 60-80years (early elderly). In the subgroup of older than 80years (oldest of old) there were 8% patients. In fact 40% of our patients were less than 65 years of age.

Hb values ranged from 2.9 to 12.6 gm/dL. No statistical difference in mean Hb values between early elderly and oldest of the old or between men and women was noted. The absence of gender related difference in Hb values in elderly compared to adult age group could be attributed to menopause in elderly women due to which their iron status is similar to that of men. Also, in their population-based study Tettamani et al found elderly women as having lower Hb concentrations than elderly men. There was a weak age-related difference in Hb concentrations (p values for both <0.0001). Hb dropped to lower values in both genders with increasing age but more markedly in women [13]. No such correlation could be made in our study.

Most of the patients had moderate anaemia (57.3%) while 36% of them had mild anaemia. Severe anaemia was the least common (6.7%) (Table-1). Tettamani *et al.*, on the other hand, found mild degree of anaemia to be the most common (83.1%) followed by moderate anaemia (15.5%) and severe anaemia (2.2%) [13]. This difference could be largely explained by the fact that while the above-mentioned study was based in community, ours was a hospital-based study.

Thus, the subjects were more likely to be seriously ill with some underlying secondary diseases explaining a greater severity of anemia.

One of the largest studies done on anaemic elderly, NHANES III attributed the causation of anaemia to nutritional deficiencies (1/3 cases), ACD (1/3 cases) and UA (1/3 cases). Half of the nutritional anemias were due to IDA while rest cases suffered from deficiencies of $VB_{12}D$ and FA deficiency [2]. Our study also revealed similar peaks: Nutritional anaemia (IDA, B_{12} and FA deficiency), ACD or anaemia of inflammation and UA, butproportion of three causes varied largely in our research.

A largest fraction of anemic cases were nutritionally deficient (49.3%) in our study. 48% patients were found to have ACD and no causes could be ascertained in 21.3% patients giving a likely possibility of unexplained anaemia. Our findings had varied from NHANES III where Nutritonal anemia, ACD and Unexplained anemia were present in almost equal proportion [2, 5, 14] while in our study nutritional anemia was the most common cause. Tettamani *et al.*, found slightly higher proportion of nutritional anemia [13]. Table-5 highlights the difference in the etiological spectrum between the study by Tettamani *et al*., and our study [13].

Our study had highest proportion of nutritional anemia observed among all previous studies (49.3%). This could be possibly due to a higher prevalence of nutritional disorders in our Indian population [15]. This study was conducted on Indian population which comprise of low to middle income group and has higher prevelance of nutritional disorders [1, 16]. NHANES III was conducted on population of United States [5]. Previously all studies were based on western or high income group countries. When this study was conducted there was no data on Indian population on AOE.

FA deficiency was found to be commoner in elderly anemics in our study. In fact, it was the most common nutritional deficiency amongst all nutritional causes (29.3%). A similar observation was also made by Lee JH [17]. Folate reserves last only for 3-4 months and folate deficiency develops rapidly [18]. Our population under study was more of low income group and more likely to have poor diet and hence developed folic acid deficiency for its reserves exhaust early. Since folic acid deficiency develops rapidly in elderly with poor diet, serum folic acid level can prove to be a good marker to predict poor diet intakeor neglected elderly early in senior citizen homes. Higher folic acid deficiencies in elderly due to poor dietary intake is also supported by Lee JH [17]. Folic acid fortification is also done in some western countries reducing prevalence of folic acid deficiency. Our study showed a slightly

higher number of cases with VB_{12} deficiency when compared with Guralnik *et al*., [5].

As compared to previous studies, our study revealed the highest percentage of ACD cases. This can be explained by the fact that ours was a hospital-based study as compared to community and population based studies by other researchers [13, 14]. The chronic diseases included various infectious disorders (47%), acute coronary syndrome (12%) and CHF. Also, overall 30.6% cases revealed more than one diagnosis for underlying anemia ($VB_{12}D$ and FA deficiency, CDA, nutritional anemia and ACD) (Figure-2).

An extensive evaluation in 16 (21.3%) patients failed to reveal any underlying cause of anaemia in our study (categorised as UA). These patients were followed up till March 2016. Only one patient was lost to follow up. Of the 15 patients, 8 were alive while 7 died. 2 out of 8 patients were re-investigated and again categorised into unexplained anaemia. Remaining 6 patients did not show any significant change in their clinical condition. They had non-transfusion dependent anaemia with no evidence of bicytopenia or pancytopenia. 87.5% of these patients were between 60-80 years and 12.5 % were above 80 years of age. There was male predilection with 13 out of 16 patients being men (p = 0.05). No other study has reported a similar significant finding. UA was largely a normocytic anemia with 12 patients (75%) and 2 patients (12.5%) each of microcytic and macrocytic anemia. Table-4 shows the mean ± SD of various hematological and biochemical parameters in UA.

In the present study, 64% patients had normocytic anaemia, 21.3% patients had microcytic anaemia and 14.7% had macrocytic anaemia. Studies by Tettamani *et al*., and Alwar *et al*., also demonstrated normocytic anaemia as the commonest morphologic type of anaemia in elderly [13, 15]. ACD was the commonest cause of normocytic anaemia in our study and IDA was the commonest cause of microcytic anemia.

Thus, our study brings to certain key findings about the spectrum of anemia in elderly which are largely different from the world literature. Role of nutritional anemia and folic acid deficiency in AOE have been highlighted in this study. Low to middle income group countries like of South East Asian Region, Eastern Mediterranean Region and Africa have high prevelance of nutritional and communicable diseases and findings of this study shall be similar in these countries. The results of this study shall be helpfull in planning health budget of low to middle income group effectively. However, this is a hospital based study and there is a need for larger a community based study.

To conclude the etiological spectrum of AOE can vary among the population with different income groups. Nutritional anaemia is the commonest cause followed by ACD and UA in countries of low to middle income group. A large number of our cases showed a combination of these causes. FA deficiency was the commonest cause of nutritional anaemia followed by IDA. Serum folic acid levels can be used as a marker to predictpoor dietary intake early in elderly. This can be useful in monitoring their diet in senior citizen homes. UA was of mild to moderate degree with predominantly normocytic normochromic type. The article provides useful information to direct health care programs on elderly especially in low to middle income group countries of South East Asian Region, Eastern Mediterranean Region and Africa.

On behalf of all co-authors, corresponding author states that there is no conflict of interest

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