IMPACT OF HAEMOGLOBIN LEVELS ON OUTCOMES IN ACUTE CORONARY SYNDROME
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ABSTRACT

BACKGROUND
It is observed that anaemia is a common problem in patients hospitalised for acute coronary syndromes. There have been reports in worldwide studies of an association between anaemia and poor prognosis in patients with Acute Coronary Syndromes (ACS).

MATERIALS AND METHODS
All consecutive patients having ST-elevation myocardial infarction, non-ST elevation myocardial infarction and unstable angina who were admitted in medicine ward, Medicine Intensive Care Unit (MICU), Cardiology Department (CRD), Cardiovascular and Thoracic Surgery (CVTS) Department and incidentally found in other departments of Acharya Vinoba Bhave Rural Hospital admitted from 1st November 2014 to 31st December 2015 at AVBRH. Total 200 patients were included in the study.

RESULTS
Our study showed an association between haemoglobin levels and mean age (p=0.0001), gender (p=0.0001), risk factors like smoking (p=0.035), tobacco (p=0.001) and Killip’s class I (p=0.0001), III (p=0.0001) and IV (p=0.0001). On distribution of the MACE’s during hospital stay stratified with Hb levels, the results of analysis by Chi-square test showed that there were statistically significant differences at various haemoglobin levels in MACE’s as post-infarction angina, heart failure, VT/VF and death (p<0.05 for all). On distribution of the MACE’s during follow up on 30th day and on 180th day stratified with Hb levels, the results of analysis by Chi-square test showed that there were statistically significant differences at various haemoglobin levels in MACE’s as post-infarction angina, re-infarction, heart failure, VT/VF and death (p<0.05 for all).

CONCLUSION
To conclude our study results, it was found during the study that anaemia as an important risk factor was strongly associated with major adverse outcomes in patients with ACS. Our study suggested that there was a statistically significant correlation between the low Hb levels and MACE’s (post-infarction angina, re-infarction, heart failure, VT/VF and death) over the study period with p values <0.05 for all the outcomes. Our study results concluded that anaemia was a strong risk factor for major outcomes and increasing severity of anaemia had correlation with MACES in ACS.

KEYWORDS
ACS, Anaemia, Haemoglobin, Outcomes.

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BACKGROUND
It is observed that anaemia is a common problem in patients hospitalised for acute coronary syndromes. There have been reports in worldwide studies of an association between anaemia and poor prognosis in patients with Acute Coronary Syndromes (ACS). Anaemia has been reported to be present in 15% of patients presenting with Acute Myocardial Infarction (AMI) and in 43% of elderly patients with AML. Anaemia is associated with a higher risk of short and long-term mortality over the entire spectrum of patients with coronary heart disease, which includes chronic stable angina, ST-Segment Elevation Myocardial Infarction (STEMI), acute coronary syndrome without ST-segment elevation (NSTE-ACS) and patients undergoing percutaneous coronary intervention. The mechanisms underlying the more serious outcomes in anaemic patients...
are not fully understood, but the evidences suggest that anaemia may decrease oxygen delivery to the at risk myocardium and increase myocardial oxygen demand through necessitating a higher cardiac output to maintain adequate systemic oxygen delivery. According to WHO, the estimated prevalence of anaemia in developing countries was 42% in women 15-59 years of age, 30% in men 15-59 years of age and 45% in adults >60 years of age. Anaemia is a major health problem in India. In the 2005-2006 National Family Health Survey (NFHS-3), a household survey aimed at having national and state representative data on population health and nutrition. The prevalence of anaemia was 55% in females aged 15-49 years and 24% in males aged 15-49 years. A better understanding of the risk associated with anaemia and ACS is thus required. This current prospective cross-sectional study is a systematic approach and a review of the previously published literature in order to summarise the available evidence and to estimate the strength of the association between anaemia and adverse outcomes in patients with ACS on admission and through 30 days and 180 days follow up.

MATERIALS AND METHODS
- All patients with ST-elevation myocardial infarction, non-ST elevation myocardial infarction and unstable angina admitted in Medicine Ward, Medicine Intensive Care Unit (MICU), Cardiology Department (CRD), Cardiovascular and Thoracic Surgery (CVTS) Department from 1st November 2014 to 31st December 2015 were studied and then followed up for 6 months from the date of their admission. It was a prospective cross-sectional observational study conducted under the Department of Medicine at AVBRH, JNMC, Sawangi, Wardha (M).
- Patients were followed up on the 30th day (1 month) and on 180th day (6 months).
- We classified anaemia according to WHO's severity grades into mild anaemia (Hb=10.1-11.9 g/dL), moderate anaemia (Hb=7.1-9.9 g/dL) and severe anaemia (Hb<7.0 g/dL).
- The baseline characters included age, gender, BMI and waist/hip ratio.

OBSERVATIONS AND RESULTS

| Baseline Characteristics and Risk Factors | Hb Levels (g%) | x² (p-value) |
|------------------------------------------|----------------|-------------|
| Mean age (years)                         | 54.66 (4.50) ± SD | 65.52 (12.60) ± SD | 59.47 (13.21) ± SD | 52.59 (13.08) ± SD | 26.13, p=0.0001* (S) |
| Male                                     | 01             | 15           | 29              | 93               | 25.33, p=0.0001* (S) |
| Female                                   | 02             | 21           | 24              | 15               |                   |
| Mean BMI (kg/m. sq.)                     | 22.90 (2.06) ± SD | 21.94 (2.67) ± SD | 22.06 (2.22) ± SD | 22.54 (1.89) ± SD | 1.09, p=0.35 (NS) |
| Mean waist-hip ratio                     | 0.94 (0.06) ± SD | 0.90 (0.04) ± SD | 0.89 (0.05) ± SD | 0.91 (0.04) ± SD | 1.39, p=0.24 (NS) |
| DM                                       | --             | 13 (36.1%)   | 20 (37.7%)      | 26 (24.1%)       | 5.63, p=0.13 (NS) |
| HTN                                      | --             | 19 (52.7%)   | 22 (41.5%)      | 45 (41.6%)       | 3.25, p=0.19 (NS) |
| Smoking                                  | 2 (66.6%)      | 05 (13.8%)   | 13 (24.5%)      | 40 (37.03%)      | 68.21, p=0.0001* (S) |
| Alcohol                                  | --             | 05 (13.8%)   | 08 (15.1%)      | 26 (24.1%)       | 4.61, p=0.20 (NS) |
| Tobacco user                             | 1 (33.3%)      | 05 (13.8%)   | 14 (26.4%)      | 40 (37.03%)      | 15.30, p=0.001* (S) |
| Killip class                             | --             | 02           | 21              | 63               | 64.43, p=0.0001* (S) |
| I                                        | 01             | 14           | 26              | 42               | 1.75, p=0.62 (NS) |
| II                                       | 01             | 19           | 05              | 03               | 40.10, p=0.0001* (S) |

Inclusion and Exclusion Criteria
All diagnosed patients of ACS were included in the study. Patients who had other comorbidities like septicaemia, septic shock, active cancers/malignancies causing low haemoglobin levels, significant renal (serum creatinine >1.5 mg%) or liver disease (serum albumin <3.5 g%), active or recent (past three months) internal bleeding, known bleeding diathesis and all other noncardiac causes of mortality, e.g. fatal traumatic injury, patients already brought dead with cause of death unknown were excluded from the study also the patients not ready to give the study consent.

Killip's Classification was used to Classify the Patients into Killip's Class I-IV According to their Clinical Findings

| Class | Clinical Features |
|-------|-------------------|
| I     | No rales.         |
|       | No third heart sound. |
|       | No signs of heart failure. |
| II    | Rales in less than half of the lung field. |
|       | Presence of 3rd heart sound. |
| III   | Rales in more than half of the lung field. |
|       | Frank pulmonary oedema. |
| IV    | Cardiogenic shock, peripheral vasoconstriction (oliguria, sweating, cyanosis). |
Table 1. Baseline Characteristics and Distribution of Level of Hb with Risk Factors (N=200)

|x²| Chi-square test,* and S=statistically significant, NS=nonsignificant, SD=standard deviation.

|                  | Mean serum creatinine | Mean serum albumin |
|------------------|-----------------------|--------------------|
|                  | 1.28 (0.25) ± SD      | 1.24 (0.17) ± SD   |
|                  | 1.24 (0.20) ± SD      | 1.24 (0.17) ± SD   |
|                  | 1.22 (0.17) ± SD      | 0.26, p=0.85 (NS)  |
|                  | 4.64 (0.56) ± SD      | 4.40 (0.39) ± SD   |
|                  | 4.45 (0.43) ± SD      | 4.39 (0.42) ± SD   |
|                  | 0.26, p=0.60 (NS)     |                    |

Table 1 shows baseline characteristics and risk factors and their correlation with haemoglobin levels showing standard deviations for mean age, BMI, waist/hip ratio, sr. creatinine and sr. albumin. Of the 200 cases, 62 (31%) were females and 138 (69%) were males. Table 1 showed that 'p' value was significant for mean age (p=0.0001), gender (p=0.0001), smoking (p=0.0001), tobacco (p=0.001) and Killip’s class I (p=0.0001), class III (p=0.0001) and class IV (p=0.0001). Table also showed that 46% of the study population was anaemic.

Table 2. Distribution of MACE's on Admission Hospital Stay Stratified with Hb Levels (N=200)

|x²| Chi-square test,* and S=statistically significant, NA=not applicable.

|                  | Hb Levels (g%)                               | X² | p value |
|------------------|---------------------------------------------|----|---------|
|                  | < / =7.0 (n=3) | 7.1-9.9 (n=36) | 10.0-11.9 (n=53) | > / =12 (n=108) |
| Post infarction angina (%) | 2 (66.6%) | 5 (13.8%) | 1 (1.8%) | -- |
| Re-infarction (%) | NA | NA | NA | -- |
| Heart Failure (%) | 1 (33.3%) | 4 (11.1%) | 1 (1.8%) | 01 (0.9%) |
| VT/VF (%) | 1 (33.3%) | 6 (16.6%) | 2 (3.7%) | 01 (0.9%) |
| Death (%) | 1 (33.3%) | 4 (11.1%) | 2 (3.7%) | -- |

Table 2 shows MACE's during hospital stay on admission in relation with Hb levels for 200 patients. Results of analysis by Chi-square test figured out statistically significant differences at various haemoglobin levels in MACE's as post-infarction angina (x²=180.40, p=0.0001*), heart failure (x²=63.91, p=0.0001*), VT/VF (x²=53.86, p=0.0001*) and death (x²=61.55, p=0.0001*).

The bar graph shows post-infarction angina (66.7%) as commonest MACE in the group with Hb</=7.0 g%.
Post-infarction angina (66.6%) was the most common MACE in the group with severe anaemia and VT/VF (16.6%) was commonest for the group with moderate anaemia.

The graph shows distribution of MACE’s with Hb levels at 30th day follow up showing outcomes were maximum in the group with Hb ≤ 7.0 g%.

Table 3 shows MACE’s on 30th day followup in correlation with Hb levels for 190 patients. On follow up at 30th day, there were 3 patients who were lost to follow up. There were 7 deaths during hospital stay on admission. There were 190 cases on 30th day.

Results of analysis by Chi-square test figured out statistically significant differences at various haemoglobin levels in MACE’s as post-infarction angina (χ²=80.89; p=0.0001*), re-infarction (χ²=145.50, p=0.0001*) heart failure (χ²=32.90, p=0.0001*), VT/VF (χ²=124.10, p=0.0001*) and death (χ²=69.45, p=0.0001*). On the follow up on 30th day, there were 15 cases with post-infarction angina, 3 cases had re-infarction, 8 cases had heart failure, 6 cases had VT/VF and 22 deaths. Death was common outcome on 30th day followup.
The graph shows distribution of MACE’s with Hb levels at 30th day followup showing outcomes were maximum in the group with Hb</=7.0 g%.

| MACE’s                  | Hb Levels (g%) | p value  |
|-------------------------|----------------|----------|
|                         | </=7.0 (n=1)   | 7.1-9.9 (n=21) | 10.0-11.9 (n=41) | >/=12 (n=97) |
| Post-infarction angina (%) | 1 (100%)       | 6 (28.5%) | 3 (7.3%) | --         |
| Re-infarction (%)         | 1 (100%)       | 4 (19.04%) | 2 (4.8%) | --         |
| Heart failure (%)          | 1 (100%)       | 9 (42.8%) | 6 (14.6%) | 3 (3.1%)   |
| VT/VF (%)                 | 1 (100%)       | 1 (4.7%)  | --        | --         |
| Death (%)                 | 1 (100%)       | --        | --        | --         |

Table 4. MACE’s on 180th Day Followup (n=160)

x²=Chi-square test, *and S=statistically significant.

Table 4 shows on follow up at 180th day. There were 8 new lost to follow up, 22 deaths at 30th day follow up. There were 160 cases on 180th day. On 180th day follow up, there were 10 patients with post infarction angina, 7 patients with re-infarction, 19 patients developed heart failure, 2 patients had VT/VF and 1 death. Results of analysis by Chi-square test figured out statistically significant differences at various haemoglobin levels in MACE’s as post-infarction angina (x²=279.2, p=0.0001*), re-infarction (x²=299, p=0.0001*) heart failure (x²=233, p=0.0001*), VT/VF (x²=375.5, p=0.0001*) and death (x²=400, p=0.0001*).
The graph shows that there was 1 patient over the study period who had all the MACE’s was having severe anaemia.

During the study period, there were 3 patients who were lost to follow up on the 30th day and 8 patients who were lost to follow up on 180th day with unknown subsequent outcomes.

Table 5. Distribution of MACE’s Stratified with Hb Levels for all Patients Over the Study Period (N=200)

| MACE’s                  | ≤ 7.0 (n=3) | 7.1-9.9 (n=36) | 10.0-11.9 (n=53) | ≥12 (n=108) | χ², p-value |
|------------------------|-------------|----------------|------------------|-------------|-------------|
| Post-infarction angina | 2 (66.66%)  | 15 (41.66%)    | 10 (18.86%)      | 6 (5.55%)   | 97.00, p=0.0001* (S) |
| Re-infarction (%)      | -           | 5 (13.88%)     | 4 (7.54%)        | 1 (0.92%)   | 11.06, p=0.01* (S) |
| Heart failure (%)      | 1 (33.33%)  | 16 (44.44%)    | 11 (20.75%)      | 7 (6.86%)   | 30.24, p=0.0001* (S) |
| VT/VF (%)              | 1 (33.33%)  | 9 (25%)        | 5 (13.88%)       | 3 (2.77%)   | 33.66, p=0.0001* (S) |
| Death (%)              | 3 (100%)    | 16 (44.44%)    | 8 (15.09%)       | 3 (2.77%)   | 38.05, p=0.0001* (S) |

x²=Chi-square test, *and S=statistically significant.

Table 5 showed that over the entire study period, there were 3 patients with severe anaemia (Hb ≤ 7.0 g%) who eventually died at the end of the study period. Results of analysis by Chi-square test figured out statistically significant differences at various haemoglobin levels in MACE’s as post-infarction angina (χ²=97.00, p=0.0001*), re-infarction (χ²=11.06, p=0.01*) heart failure (χ²=30.24, p=0.0001*), VT/VF (χ²=33.36, p=0.0001*) and death (χ²=38.05, p=0.0001*).
Results of analysis by Chi-square test figured out statistically significant differences at various study duration in outcomes as heart failure \((p=0.032^*)\) and death \((p=0.0024^*)\), while the differences were insignificant for post-infarction angina, re-infarction and VT/VF.

| Unstandardised Coefficients | Standardised Coefficients | t-value | p-value |
|-----------------------------|---------------------------|---------|---------|
| **B** | **Std. Error** | **Beta** | **t**-value | **p**-value |
| Hb\% | 20.721 | 3.784 | -0.204 | 3.216 | 0.002*, S |
| Age | -0.037 | 0.012 | -0.266 | 3.804 | 0.0001*, S |
| Gender | -1.379 | 0.363 | 0.011 | 0.170 | 0.866, NS |
| BMI | 0.013 | 0.075 | -0.393 | 0.629 | 0.530, NS |
| W/H ratio | -1.894 | 3.013 | -0.039 | 0.061 | 1.000, 0.318, NS |
| DM | 0.321 | 0.321 | -0.306 | 0.498 | 0.619, NS |
| HTN | -0.144 | 0.288 | 0.004 | 0.063 | 0.950, NS |
| Smoking | -0.243 | 0.347 | -0.406 | 0.699 | 0.485, NS |
| Alcohol | 0.024 | 0.377 | -0.030 | 0.303 | 0.478 | 0.633, NS |
| Tobacco | 0.158 | 0.330 | -0.402 | 6.242 | 0.0001*, S |
| Killip's class | -1.286 | 0.206 | 0.097 | 1.652 | 0.100, NS |
| Sr. albumin | -1.277 | 0.773 | 0.012 | 0.207 | 0.836, NS |
| Sr. creatinine | 0.069 | 0.332 | -0.039 | 0.629 | 0.530, NS |

Table 7. Multiple Regression Logistic Analysis

*and S=statistically significant, NS=non-significant.

Multiple regression logistic analysis was done using dependent parameters (gender, mean age, BMI, waist/hip ratio, sr. albumin, sr. creatinine, smoking, DM, HTN, tobacco, alcohol and Killip’s class), which suggested that p-value was statistically significant for age, gender and Killip’s class, which showed that age, gender and Killip’s class were statistically significantly associated with haemoglobin and affected the haemoglobin level.

**DISCUSSION**

Our study was conducted under Medicine Department at AVBRH, Sawangi (M) Wardha.

**Baseline Characteristics and Distribution of Level of Hb with Risk Factors** - In a study by Quan-Zhou Feng et al\(^9\) in China showed that age, diastolic pressure, pulse pressure, TG, albumin, creatinine and LVEF were significantly associated with haemoglobin concentration.

In comparison to the above study, our study showed an association between haemoglobin levels and mean age \((p=0.0001)\), gender \((p=0.0001)\), risk factors like smoking \((p=0.0001)\), tobacco \((p=0.001)\) and Killip class I \((p=0.0001)\), II \((p=0.0001)\) and IV \((p=0.0001)\).

No association was found between sr. creatinine and sr. albumin levels with haemoglobin in our study.

Stefan D. Anker et al\(^10\) showed that lower haemoglobin at baseline was associated with female gender and the presence of diabetes, higher age and Killip’s class, lower body mass index, systolic blood pressure, total cholesterol and the absence of current smoking (all \(p<0.05\)).

In comparison with the above study, our study also had an association between mean age \((p=0.0001)\), gender \((p=0.0001)\), smoking \((p=0.0001)\), tobacco \((p=0.001)\) and Killip class I \((p=0.0001)\), II \((p=0.0001)\) and IV \((p=0.0001)\) with haemoglobin. No association was found for BMI and diabetes with haemoglobin levels in our study.

**Distribution of MACE’s on Admission Hospital Stay Stratified with Hb Levels** - On distribution of the MACE’s during hospital stay stratified with Hb levels, the results of analysis by Chi-square test showed that there were statistically significant differences at various haemoglobin levels in MACE’s as post-infarction angina \((x^2=180.40, p=0.0001^*)\), heart failure \((x^2=63.91, p=0.0001^*)\), VT/VF \((x^2=53.86, p=0.0001^*)\) and death \((x^2=61.55, p=0.0001^*)\).

Post-infarction angina \((66.6\%)\) was the most common MACE in the group with severe anaemia and VT/VF \((16.6\%)\) was commonest for the group with moderate anaemia.

**Distribution of MACE’s on 30th Day Stratified with Hb Level** - In our study, the distribution of MACE’s on 30th day follow up stratified with Hb level. The results of analysis by Chi-square test figured out that there were statistically significant differences at various haemoglobin levels in MACE’s as post-infarction angina \((x^2=80.89, p=0.0001^*)\), re-infarction \((x^2=145.50, p=0.0001^*)\) heart failure \((x^2=32.90, p=0.0001^*)\), VT/VF \((x^2=124.10, p=0.0001^*)\) and death \((x^2=69.45, p=0.0001^*)\).

% of MACE’s were equal for all outcomes \((50\%)\) in the group with severe anaemia.

Death was commonest MACE in groups with moderate and mild anaemia with 34.3% and 13.3%, respectively.

In the study by Sebatine et al\(^8\) they had statistically significant \(p\) values for all the major endpoints with STEMI (cardiovascular death, congestive heart failure and composite events) \(p<0.001\) for each endpoint and with NSTEMI (cardiovascular death, myocardial re-infarction, recurrent ischaemia and composite) \(p<0.001\) for each endpoint.

On comparing with the results of above study, in our study, similar results were found with significant \(p\)’ value \((p=0.0001)\) for each MACE’s (post-infarction angina, re-infarction, heart failure, VT/VF and death).
Distribution of MACE’s on 180th Day Stratified with Hb Level- On distribution of MACE’s on 180th day, the results by Chi-square test figured out statistically significant differences at various haemoglobin levels in outcomes as post-infarction angina \((x^2=279.2, p=0.0001*)\), re-infarction \((x^2=299, p=0.0001*)\), heart failure \((x^2=233, p=0.0001*)\), VT/VF \((x^2=375.5, p=0.0001*)\) and death \((x^2=400, p=0.0001*)\).

The commonest MACE for group with moderate anaemia, mild anaemia and for normal Hb was heart failure with 42.8%, 14.6% and 3.1%, respectively.

Distribution of MACE’s Stratified with Hb Levels for all the Patients Over the Study Period- In our study, the MACE’s over the entire study period on stratifying with Hb level, the results of analysis by Chi-square test showed statistically significant differences at various haemoglobin levels in MACE’s as post-infarction angina \((x^2=97.00, p=0.0001*)\), re-infarction \((x^2=11.06, p=0.01*)\) heart failure \((x^2=30.24, p=0.0001*)\), VT/VF \((x^2=33.36, p=0.0001*)\) and death \((x^2=38.05, p=0.0001*)\).

MACE’s on Admission Hospital Stay and Follow up- In our study, on correlating outcomes/MACE’s and follow up duration (on admission hospital stay, on 30th day and on 180th day), the results of Chi-square test analysis showed statistically significant differences over the study duration in outcomes as heart failure \((p=0.032*)\) and death \((p=0.0024*)\), while the differences were insignificant for post-infarction angina, re-infarction and VT/VF.

As the prevalence of anaemia in developing countries was 42% in women 15-59 years of age, 30% in men 15-59 years of age and 45% in adults >60 years of age, occurrence of MACE’s had similar presentation in our study.

Our study also showed that the factors like age, gender, smoking, tobacco and Killip’s class (I, III and IV) were statistically associated with Hb and affected haemoglobin levels significantly.

CONCLUSION

Our study results found out a statistically significant correlation between the low Hb levels and MACE’s (post-infarction angina, re-infarction, heart failure, VT/VF and death) over the study period, with \(p\) values <0.05 for all the outcomes over the study period.

To summarise our study results in a nutshell, study results found that lower Hb levels on admission had a significant impact on MACE’s in patients with ACS and was associated with adverse outcomes across the spectrum of ACS and anaemia was a strong risk factor for major outcomes and increasing severity of anaemia had correlation with MACES in ACS.

Limitations

1. The sample size \((n=200)\) was less and duration of our study was short.
2. There were 11 patients who were lost to follow up, their outcomes were not known.

3. The cause of anaemia in the patients of this present study was not known, the different causes might have residual confounding.

4. Lipid profile as a baseline character was not used in our study due to technical errors.

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