Iron Deficiency Anemia as a Risk and Prognostic Factor of Community Acquired Pneumonia

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Abstract

Background: Community Acquired Pneumonia (CAP) is a major cause of morbidity and mortality. While there is much data about risk factors for severe outcome in the general population, there is less focus on iron deficiency anemia as a risk and prognostic factor among these patients. Therefore, we aimed to detect simple prognostic factors for severe morbidity and mortality in patients with CAP.

Patients and Methods: This study was done on 110 patients with ages ranged between 35 and 60 years who were diagnosed with CAP (defined as pneumonia identified in persons who have not been hospitalized recently). This study was carried out in Internal Medicine and Chest Departments, Al-Azhar Assiut University Hospital, over a period from April 2013 to January 2014. CRP, CBC and iron profile were done for all patients.

Results: The cohort included 110 patients with mortality rate was 8.18% (9 cases) and the mean length of stay was 16.22±1.25 days. In univariate analysis, patients those with co-morbid conditions tended to have complicated disease. In multivariate analysis, variables associated with complicated hospitalization included Blood Urea Nitrogen (BUN) >30 mg/dL, creatinine >1.3 mg/dL, CRP >6mg/L, Hb <1 1g/dL, abnormal White Blood Cells (WBC) and elevated RDW. Iron level was decreased in complicated than uncomplicated cases (32.47±7.43 vs 57.72±8.65ug/dL) (p<0.001). TIBC was lower in complicated than uncomplicated cases (225.04±15.26 vs 257.10±9.84ug/dL) (p<0.001), with increase in serum ferritin in complicated than uncomplicated cases (70.21±13.94 ng/mL) (p<0.001). Serum iron showed negative linear correlation with CRP (r=-0.765; p<0.0001) and ferritin (r=-0.658; p<0.0001).

Conclusions: Iron deficiency is common in patients with CAP and it is associated with significant higher rates of mortality and severe morbidity. RDW is a good and cheap prognostic marker for CAP on admission. There is an excellent inverse correlation between serum iron and CRP during decline in infection.

Key Words: C-reactive protein – Community acquired pneumonia – Ferritin – Iron – TIBC.

Introduction

COMMUNITY-Acquired Pneumonia (CAP) is a syndrome in which acute infection of the lungs develops in persons who have not been hospitalized recently and have not had regular exposure to the health care system [1]. Pneumonia is referred to as the forgotten killer. It is the most common infectious cause of death in the world (the third most common cause overall), with almost 3.5 million deaths yearly [2].

If CAP severe enough to require hospitalization, it is associated with excess mortality over the subsequent years among survivors [3]. Admission to the hospital for CAP is also costly, especially if care in an Intensive Care Unit (ICU) is required [4].

Much research has been conducted in recent decades to determine prognostic factors for adverse outcome in patients hospitalized for CAP, including concomitant diseases and laboratory parameters on admission [8].

Iron Deficiency Anemia (IDA) is the most common nutritional disorder, affecting more than one-third of the general population [6].

The presence of IDA may have multifaceted clinical consequences, not only directly related to impaired erythropoiesis, but also to marked impairment of oxidative metabolism, cellular energetics, and cellular immune mechanisms [7]. Iron deficiency with and without anemia is accompanied by reduced aerobic performance and subjective complaints of poor physical condition [8].

Whatever the etiology of anemia, the relation between it and CAP has not been fully evaluated, and only few reports are available evaluating this subject [9].
Therefore, our aim was to determine the risk and prognostic effect of IDA that is associated with CAP complicated hospitalization.

**Patients and Methods**

This study was done on 110 patients [63 males (57.3%) and 47 females (42.7)]. Their ages ranged between 35 and 60 years with mean ± SD 53.17 ± 3.53. This study was carried out in Internal Medicine Department, Assuit University Hospital, Al-Azhar University, over a period from April 2013 to January 2014. The study protocol was approved by the local ethics committees, and all patients gave adequate informed consent.

CAP was defined as the presence of a new infiltrate on the chest radiograph along with appropriate clinical history and physical signs of lower respiratory tract infection in a patient not hospitalized within the previous month. The typical pneumonia diagnosed by a newly recognized lung infiltrate on chest imaging together with fever, cough, sputum production, shortness of breath, physical findings of consolidation, and leukocytosis [10]. Some cases were complaining of confusion and pleuritic chest pain and some of them do not cough, produce sputum, or have an elevated white-cell count [11].

Patients were subclassified into two groups according to absence or present of complication. Complicated hospitalization was defined as at least one of the following parameters: Hospitalization longer than 10 days, admission to ICU and inhospital mortality. Otherwise, the hospitalization was defined as uncomplicated.

Exclusion criteria included transfer from another hospital, hospitalization for any cause other than CAP during the 30 days prior to admission, hospital-acquired pneumonia (defined as pneumonia which was diagnosed more than 48 hours after admission) or partial antibiotic treatment before admission.

**All patients were asked on the following:**

1- Malignancies: Solid tumors, hematologic malignancies.
2- Pulmonary diseases: Bronchial asthma, chronic obstructive lung disease, interstitial lung disease, bronchiectasis, permanent tracheostomy, lung malignancy, past history of thoracic radiotherapy, previous episode of pneumonia, and previous or current active smoker.
3- Immune suppression conditions: Current chronic corticosteroid treatment, current or recent chemotherapy treatment, primary immune deficiency, history of blood transfusion.
4- Cardiovascular diseases.
5- Chronic kidney disease.
6- Diabetes mellitus.
7- Chronic liver diseases.
8- Prior neurologic damage.

**All patients were subjected to the following:**

- Full history taking.
- General examination and local chest examination.
- Plain chest X-ray.
- Direct smear examination with Ziehl-Neelsen staining for the diagnosis of tuberculosis.
- Body Mass Index (BMI) was calculated by dividing the weight (kg) by height² (m²).
- Arterial blood pressure was measured by mercury sphygmomanometer.
- Measurement of C-reactive protein (by AVITEX CRP-rapid latex agglutination test kit for the detection of CRP in human serum).
- Complete Blood Counts (CBCs) using automated cell counter Swelab®, Sweden, haemoglobin concentration (g/dL) and red cells distribution width (RDW%).
- Quantitative determination of glucose was done by Glucose Oxidase (GOD) test in presence of peroxidase (POD) (SPINREACT®, SAU, Spain).
- Blood urea was measured by Berthelot, Enzymatic colorimetric (Diamond, MDSS GmbH, Germany). Blood Urea Nitrogen (BUN) was calculated by dividing the value of blood urea on 2.14.
- Serum creatinine measured by RANDOX kit, Co. Antrim, United Kingdom.
- The following iron biomarkers were assessed directly: Serum concentrations of iron (µg/dL), ferritin (ng/mL), and total iron-binding capacity (TIBC, µg/dL). Serum ferritin was measured using immunoassay based on electrochemiluminescence on the VIDAS System (VIDAS® Ferritin bioMérieux). Serum iron and TIBC were assessed using a substrate method with Feren S (Thermo Fisher Scientific, Waltham, MA, USA).

**Specimen collection and preparation:**

Blood samples were taken from the patients using wide-bore needle and withdrawn slowly from antecubital vein to avoid hemolysis of RBCs by careful vein puncture. These samples were divided
Statistical analysis:

Data was described as mean ± SD/SE and percentages. Least significant difference for intergroup variance was measured at 95% confidence interval. The metric data was analyzed by student’s t-test, while Pearson coefficient of linear correlation was used to describe the level of correlation between CRP, serum iron and ferritin. Two-tailed p-values of 0.05 or less were considered as statistically significant. All statistical analyses were performed using SPSS (Statistics Products Solutions Services, New York, USA) 17.0 software for Windows; Redmond, Washington, USA.

Results

The cohort included 110 patients; 57.3% were males, mean age were 53.17 ± 3.53 years, the in-hospital mortality rate was 8.18% (9 cases) and the mean length of stay was 16.22 ± 1.25 days for all cases (5.31 ± 1.42 and 27.54 ± 3.25 days in uncomplicated and complicated patients, respectively).

Univariate analysis of complicated hospitalizations as shown in (Table 1), 42 patients (38.18%) experienced complicated hospitalization; patients those with co-morbid conditions tended like concomitant diabetes, chronic liver diseases, interstitial lung diseases heart diseases, elevated CRP levels, anemia and abnormal WBC had a complicated hospitalization (p<0.05). While patients who had disturbed chronic renal failure did not have a more complicated course of CAP (p>0.05).

Complicated cases have lower iron and TIBC and higher ferritin levels when compared to uncomplicated cases recording 32.47 ± 7.43 µg/dL, 225.04 ± 15.26 µg/dL and 70.21 ± 26.78ng/mL for iron, TIBC and ferritin respectively in complicated cases and 57.72 ± 8.65 µg/dL, 257.10 ± 9.84 µg/dL and 30.25 ± 13.94ng/mL for iron, TIBC and ferritin respectively in uncomplicated cases.

We found a statistically significant inverse correlation between CRP and iron levels r=−.765, p<0.0001, and inverse correlation between iron and ferritin levels r=−.658, p<0.0001.

| Table (1): Baseline characteristics of the cohort with univariate analysis of risk factors for detection of complicated CAP patients. |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                | All studied patients (n:110) | Uncomplicated cases (n:68) | Complicated cases (n:42) | t-test/Odds ratio (95% CI) | p-value |
| Age (years)                    | Mean±SD                        | Mean±SD                        | Mean±SD                        |                                  |        |
| Males/females (No)             | 63/47                          | 42/26                          | 21/21                          | 1.615 (0.742-3.516)              | 0.088  |
| BMI Kg/m²                      | 26.5±4.4                      | 27.0±4.3                      | 26.2±4.5                      | 1.009                           | 0.042  |
| Hospital stay in days          | 16.2±2.12                      | 5.3±1.42                      | 27.5±3.25                     | 9.251                           | <0.0001 |
| Co-morbid conditions           |                                |                                |                                |                                  |        |
| Diabetes mellitus              | 26 (23.6%)                     | 9 (13.2%)                      | 17 (40.5%)                     | 4.74 (3.13-7.16)                | <0.001 |
| Chronic renal failure          | 8 (7.27%)                      | 2 (2.94%)                      | 6 (2.52%)                      | 2.07 (0.930-4.594)              | 0.075  |
| Chronic liver diseases         | 21 (19.1%)                     | 8 (11.8%)                      | 13 (30.1%)                     | 1.88 (1.063-3.310)              | 0.030  |
| Lung disease*                  | 34 (30.9%)                     | 18 (26.5%)                     | 16 (38.1%)                     | 1.61 (1.115-2.337)              | 0.011  |
| Heart diseases                 | 5 (4.5%)                       | 1 (1.47%)                      | 4 (9.52%)                      | 2.66 (1.54-4.56)                | <0.001 |
| HR/min                         | 86.7±20.3                      | 86.8±20.6                      | 86.7±20.1                      | 0.998                           | 0.254  |
| SBP (mmHg)                     | 137.3±32.5                     | 137.9±36.1                     | 136.6±29.0                     | 1.009                           | 0.147  |
| RBS >200mg/dL                  | 33 (30.0%)                     | 15 (22.05%)                    | 18 (42.6%)                     | 1.77 (0.903-3.454)              | 0.096  |
| BUN >30mg/dL                   | 12 (10.9%)                     | 5 (7.35%)                      | 7 (16.7%)                      | 2.62 (1.552-4.422)              | <0.0001 |
| Creatinine >1.3mg/dL           | 14 (12.7%)                     | 6 (8.82%)                      | 8 (19.05%)                     | 1.89 (1.183-3.031)              | 0.007  |
| CRP >6mg/L                     | 71 (64.5%)                     | 41 (60.3%)                     | 30 (71.4%)                     | 1.58 (1.082-2.305)              | 0.018  |
| WBCs <4 or >12x10⁹/L           | 62 (56.4%)                     | 35 (51.5%)                     | 27 (64.3%)                     | 1.68 (1.174-2.416)              | 0.005  |
| Hb <11g/dL                     | 61 (55.45%)                    | 30 (44.11%)                    | 31 (73.8%)                     | 2.11 (1.375-3.229)              | 0.001  |
| RDW >14.5%                     | 41 (37.3%)                     | 18 (26.5%)                     | 23 (54.8%)                     | 3.49 (2.419-5.023)              | <0.0001 |
| Iron µg/dL                     | 48.08±14.78                    | 57.72±8.65                     | 32.47±7.43                     | 15.66                           | <0.0001 |
| TIBC µg/dL                     | 244.86±19.79                   | 257.10±9.84                    | 225.04±15.26                   | 13.39                           | <0.0001 |
| Ferritin ng/mL                 | 45.51±27.74                    | 30.25±13.94                    | 70.21±26.78                    | 10.27                           | <0.0001 |

* Includes: bronchial asthma, chronic obstructive lung disease, interstitial lung disease, bronchiectasis, permanent tracheostomy, lung malignancy, past history of thoracic radiotherapy, previous episode of pneumonia, and previous or current active smoking.
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Discussion

Few reports are available in literature regarding the role of iron deficiency anemia per se, as a risk factor and prognostic for CAP. In our study, low hemoglobin level was found to be a risk factor for CAP as it was detected in 73.8% of complicated cases, 44.11% of uncomplicated cases and 55.45% of all patients \((p=0.001)\). It is feasible to recollect the normal functions of hemoglobin; it facilitates oxygen \((O_2)\) and carbon dioxide \((CO_2)\) transport. It caries and inactivates Nitric Oxide (NO) and also play the role of a buffer [12]. Tissue oxygen buffer' function is very important one of hemoglobin system. Hemoglobin in the blood is mainly responsible for stabilizing the oxygen pressure in the tissues [13]. Quantitative and/or qualitative reduction in Hb, may adversely affect the normal functions.

These data came in concordance with the study done by Harris et al., [14]. They studied anemia and air pollution as risk factors for ARLTIs. They found that anemic patients are at increased risk of acute respiratory infection hospitalization. Bhaskaran et al., [15] in a study of 43 patients had found 83% with pneumonia had hemoglobin less than 11 g/dL. In another study of iron deficiency anemia and respiratory infection by De-Silva et al., [16] an over all prevalence of anemia was found in 52.6%.

The prevalence of anemia in our study was 55.45% among all patients, even among those without complication, this may due to the facts that some degree of anemia has already occurred in CAP patients at the time of presentation, due to repeated blood draws or the dilutional effects of intravenous fluids could explain low hemoglobin levels. The decline in hemoglobin values that occurred over the first few days of hospitalization is consistent with that seen in every admitted patients, where hemoglobin values may decline by >0.5g/dL/day in non-bleeding patients [17,18]. These changes are believed to be due not only to dilutional effects of fluids and frequent blood draws [19], but also to the effects of inflammatory cytokines, inadequate red cell production, and excessive red cell destruction [20].

In our study, the presence of anemia was an additional risk factor associated with increased mortality after accounting for factors such as comorbidity, initial illness severity, the development of severe sepsis, and use of mechanical ventilation. This association persisted when limited to hospital survivors. Other studies of CAP patients have identified anemia as a risk factor for mortality [21-24] and an initial hematocrit level of <30% is a component of the Pneumonia Severity Index (PSI) [25], which classifies 30 day mortality risk. Yet, does the anemia actually cause increased mortality or is it merely an additional marker of illness severity, and therefore, mortality?

Red Blood Cell Distribution Width (RDW) is a laboratory index used in the differential diagnosis of microcytic anemia. Recently, several studies showed that a high RDW index predicts severe morbidity and mortality in various cardiac conditions [26-28].

Ku et al., [29] demonstrated recently that RDW is an independent predictor of mortality among patients with gram-negative bacteremia. While in pulmonary diseases, current study shows that in patients with CAP, elevated RDW levels on admission either alone or in combination with abnormal levels of WBC are associated with significant higher rates of mortality and complicated hospitalization. As regard to RDW levels, 54.8% of complicated cases were susceptible compared to 26.5%

Fig. (1): Inverse correlation between CRP and serum iron levels.

Fig. (2): Inverse correlation between serum iron and ferritin levels.
of uncomplicated cases. Concordant with our findings, Wang et al., [30] reported recently that a graded independent relation between higher RDW and adverse outcomes in CAP patients admitted to ICU.

Lee et al., [31] demonstrated in 744 patients that elevated RDW on admission was associated with increased 30-day mortality, length of hospital stay, and use of vasopressors in hospitalized patients with CAP. The inclusion of RDW improved the prognostic performance of the PSI and CURB-65 scores.

The mechanism underlying the association between high levels of RDW and adverse outcome in patients hospitalized with pneumonia is unknown. Several explanations were suggested to this surprising finding. Abnormal RDW usually suggests one or more chronic condition that accompanies significant complicated CAP, such as anemia or nutritional deficit. Another mechanism that was suggested is the release of cytokines in response to inflammatory stress. These cytokines block the activity of erythropoietin and cause production of ineffective red blood cell and elevated RDW [32,33]. Lippi et al., [34] found a correlation between high RDW and elevated indexes of inflammation (Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP)). This correlation was independent of concomitant diseases, and was demonstrated even when anemic patients were excluded from the statistical analysis.

Our data demonstrated that RDW is a valuable and sensitive marker for a high level of inflammatory activity in young patients with CAP.

In current study, iron was lowered in complicated cases (32.47 ±7.43 µg/dL), compared to (57.72 ±8.65 µg/dL) in uncomplicated cases and (48.08 ±14.78 µg/dL) in all patients (p<0.0001). Also TIBC was lowered in complicated cases (225.04 ±15.26 µg/dL), compared to (257.10 ±9.84 µg/dL) in uncomplicated cases and (244.86 ±19.79 µg/dL) in all patients (p<0.0001). This may explained by the fact that, cell and tissue damage resulting from an oxidative stress can ultimately be the consequence of a disruption of normal iron metabolism and an increased availability of catalytically active metal [38]. Measured serum iron concentration is principally the Fe3+ bound to serum transferrin and does not include the iron contained in serum as free hemoglobin [36].

Moreover, experimental and epidemiological evidence suggests that iron is required for proper immune function. Iron deficiency has been shown to compromise cell-mediated immunity, decreasing T-cell numbers and proliferative response and potentially reducing macrophage activity [37], which may reduce host capacity to control infection. Iron status may also modulate the type of immune response mounted through its influence on the body’s cytokine profile [38].

Ferritin was increased in complicated cases (70.21 ±26.78ng/mL), compared to (30.25 ±13.94 ng/mL) in uncomplicated cases and (45.51 ±27.74 ng/mL) in all patients (p<0.0001). Elevations of serum ferritin levels have been associated with a variety of infectious and noninfectious disorders) [39]. Elevations in serum ferritin level (<2 times the normal value) may occur with a variety of disorders as part of the acute-phase response [40]. Acute-phase elevations in serum ferritin levels (<2 times the normal value) occur early and transiently [41]. However, highly elevated and/or sustained serum ferritin levels (>2 times the normal value) should not be ascribed to the acute-phase response and are reflective of the underlying process [42].

Our study shows that there is an excellent inverse correlation between serum iron and CRP (r=–0.765; p<0.0001) and ferritin (r=–0.658; p<0.0001). CRP production is rapidly stimulated, rises early before the onset of clinical symptoms, and declines with the resolution of infection. This acute phase protein could be used as a tool for monitoring the effect of antibiotic therapy and decline in infection. Humans respond to infection with inflammatory cytokine induced hypoferremia [43]. This result was in agreement with Borovac et al., [44] study that found excellent correlation between serum iron and Acute Phase Proteins (APPs) where serum iron showed inverse correlation with CRP (r=–0.625; p<0.01). With the resolution of condition, they got increase of serum iron and normalization of CRP level.

Limitations of current study:

• The major limitation of our study is that it was planned to detect the association between iron deficiency anemia (low hemoglobin, iron and ferritin with higher TIBC and RDW levels) and prognosis of CAP; however, we did not examine whether this observation is unique to CAP or could be demonstrated in other inflammatory and infectious states.

• Very few subjects in our study had positive blood or sputum cultures and cultures were not universally drawn, which is typical for observational studies of CAP [45,46]. Consequently, we could not reliably determine whether the prevalence or
severity of anemia varied by presence of bacteremia or by type of infecting organism.

- We did not have access to pre-CAP hemoglobin levels, and were therefore unable to determine if anemia preceded the development of pneumonia. Consequently, though our anemia prevalence rates for the entire hospital stay are accurate; our results may be either over or underestimated depending on hemoglobin values for those who were not sampled that day.

Conclusion:

Iron deficiency is common in patients with CAP. It is associated with significant higher rates of mortality and severe morbidity. The value of serum ferritin increases with the resolution of condition. RDW is a good and cheap prognostic marker for CAP on admission. There is an excellent inverse correlation between serum iron and CRP during decline in infection. Whether prevention or treatment of CAP-associated anemia would improve clinical outcomes remains to be seen.

References


المفحص العربي

يعتبر الالتهاب الرئوي المكتسب عن طريق المجتمع من أكثر الأمراض انتشارا والسامة للوفاة، وذلك دراسات عديدة عن العوامل المسببة لهذا المرض ولكن لا يحظى عامل أمميا مقص الجديد بالقدر الكافي من الدراسة حيث يعتبر العديد من أهم العناصر الهامة للإصابة بالداء، والذي يلعب دورًا حيويًا في تحديد الالتهاب الرئوي المكتسب عن طريق المجتمع وذلك عن طريق قياس مستوى الحديد ومخزونه والسعة الكلية لتشبع الحديد لدى المرضى المصابين.

أجريت هذه الدراسة على مائة وعشر مريضاً يعانون من التهاب الرئوي المكتسب عن طريق المجتمع ولم يتم حجزهم بلتحديد المستشفيات حديثًا. توزعت أعمارهم بين الخامسة والعشرين والسنين عامًا ثم احتجزهم بقسم الباطنة العامة تقدم الأمراض الصدرية بمستشفي طب الأزهر بأسوان في الفترة من شهر أبريل 2013 إلى شهر يناير 2014. وذلك بعد اخذ الموافقة المناسبة منهم للاشتراك في هذه الدراسة.

تم تقسيم المرضى إلى مجموعتين بناءً على حدوث أو عدم حدوث مضاعفات لدى هؤلاء المرضى. بعد أخذ التاريخ المرضي والشخصي والعائلي والفحص الكلينيكي الشامل ثم عمل صورة في كاملاً وقياس مستوى عامل البروتين التفاعلي (CRP) ومستوى الحديد ومخزون الحديد والسعة الكلية لل الحديد.

أوضحت الدراسة الإحصائية النتائج الآتية:

- تضاعف حالات وفيات بمعادل 8.2٪.
- متوسط بقاء المريض بالمستشفى 25 2±6 2 يوم.
- ارتفاع نسبة حدوث مضاعفات للمريض الذين لديهم عوامل مرضية أخرى مثل ارتفاع نسبة نيتروجين البوليا سيل يملأ أكثر من 200 mg/dL30.5٪، وارتفاع مستوى الكرياتينين أكثر من 20 mg/L1.3٪، وانخفاض مستوى الهيموجلوبين (CRP) وارتفاع مستوى البروتين التفاعلي (CRP) أكثر من 11 mg/dL11.1٪. أقل من 30٪ .
- انخفاض مستوى الحديد، وسعة ارتباط الحديد الكلية لدى الذين يعانون من التهاب الرئوي مكتسب عن طريق المجتمع والمصابوب بحروف
- مضاعفات مقارنة بالمجموعة الأخرى.
- ارتفاع مستوى مخزون الحديد (CRP) لدى الذين يعانون من التهاب الرئوي مكتسب عن طريق المجتمع والمصابوب بحروف
- مقارنة بالمجموعة الأخرى.
- وجود ارتباط إحساسي سلبي بين مستوى الحديد وكل من عامل البروتين التفاعلي (CRP) ومستوى مخزون الحديد (CRP).

وقد خلصت الدراسة إلى أنه على الرغم من وجود علاقة بين مستويات الحديد والتهاب الرئوي المكتسب عن طريق المجتمع إلا أنه نقص العوامل الأمراضية يساعد على الشفاء، مع بعض الأدوات التي تحتوي على العديد بسبب الآلية الأولى لزيادة نمطية جدية للدراسة.