Dear Editor,

Anemia occurs commonly worldwide and at all ages of life and, although frequently overlooked, it affects mortality, morbidity, and quality of life, even when mild. The prevalence of anemia varies widely depending on its definition. The World Health Organization has established some cut-off hemoglobin (Hb) levels, stratified by gender and in part by age, to define the presence of anemia. For adults, these levels are less than 12 g/dL for women and less than 13 g/dL for men, although these cut-off points may not be fully appropriate for the elderly. Severe anemia has been defined as Hb <8.0 g/dL for both genders. However, hemoglobin is a simple surrogate marker for the disease that has provoked anemia. To treat anemias simply restoring a “safer” hemoglobin level (i.e., by means of transfusions or erythropoietin) may be very different than curing them by eliminating the causes that had provoked the condition. Moreover, several reports have shown that both transfusions and erythropoiesis stimulating agents may indeed carry an increased risk of adverse events. Therefore, it is quite surprisingly that in health services, anemia continues to be regarded as a “minor” disease, even when severe, to be assigned to the ambulatory setting in the absence of a robust body of literature to support this common practice.

In Italy, disorders of red blood cells in people older than 17 years [International Classification of Diseases – ninth revision Clinical Modification (ICD-IX-CM) codes 280–285] “outside urgencies” are considered not to be appropriate for hospital admission, regardless of the severity of the Hb deficiency or the presence of important comorbidities, including a reduced functional capacity in older people. We believe that to rely on assumptions of this kind in advance of evidence may carry a risk to induce some potentially deleterious consequences, including overuse of blood transfusions to reach an Hb level “safe” for emergency room discharge rather than patient clinical status. Historically, and in current guidelines, the indication for transfusion comes from both Hb concentration and the clinical scenario; to transfuse in order to avoid hospital admission should be regarded as unethical.

We conducted an observational, prospective study of all patients admitted to an Internal Medicine ward with very severe anemia, aiming to explore the clinical and assistential burden of severely anemic patients admitted to the hospital. Patients with an Hb concentration of 6 g/dL or less were eligible. Those presenting with overt hemorrhage or acute anemia were excluded. Patients were managed as usual, and no diagnostic or therapeutic procedure was performed for study purposes alone. In defining the main diagnosis at discharge, our standard procedure was to select first the procedure that had absorbed the largest amount of resources, accordingly to a predefined hierarchy (Table 1) and then to choose the consequent diagnosis. Accordingly to our laboratory, we defined microcytic anemia as all cases with a mean corpuscular volume (MCV) of less than 81 fL, and macrocytic anemia as those with a MCV of more than 98 fL and normocytic anemia as all others. Thrombocytopenia was defined as an absolute platelet count of less than $150 \times 10^9$/L; leukopenia as a white blood cell absolute count of less than $4.0 \times 10^9$/L and lymphopenia as an absolute lymphocyte count of less than $1.1 \times 10^9$/L.

The main outcome of the study was all-cause, in-hospital mortality. Secondary outcomes were one-year mortality and the percentage of admissions for anemia that were lost to a retrospective analysis based only on coding. Continuous variables are expressed as means ± standard deviation (SD) or as medians with minimum and maximum values when data did not have a normal distribution; categorical data are given as counts and percentages. The Institutional Review Board approved the study, which was carried out and is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.

Between October 2009 and June 2015, 86 patients were admitted for very severe anemia. Of these, 61 (71%) were women and 25 (29%) were men; eight patients (9.3%) came from nursing homes, one from a prison and the remaining cases were from home. The mean age was 76.8 ± 15.6 (range: 33–100). Seventy-one patients (82.5%) were 65 years or older. Nine of the patients (six women and three men) died during...
hospitalization (10.5%); the remaining 77 patients were discharged and followed up for about 170 patient-years. Deceased patients were older than discharged patients: mean age was 90 ± 10 vs. 75.5 ± 15.7 (p-value < 0.01). During the same period, general in-hospital mortality was 12.3%. Mean follow-up was 806 days (range: 16–2072 days) during which time 32 more patients died. Mean time to death was 412 days. The cumulative percentages of death at 1, 3 and 12 months were 3.9%, 13.0% and 29.9%, respectively. When in-hospital mortality was included and added to one-month mortality, the corresponding figures became 13.9%, 22.1% and 37.2%. Hematological data are shown in Table 2. There were no significant differences in mean Hb and MCV, or in the presence of cytopenias other than anemia. However, discharged patients more often had microcytic anemias (54.5%) compared to deceased patients, whose anemias were more often normocytic or macrocytic (77.8%). Patients with a normocytic anemia had an increased risk to die in the hospital when compared with those with microcytic anemia.

### Table 2 – Hematological data.

|                  | Discharged 77 (89.5%) | Deceased 9 (10.5%) | p-Value |
|------------------|-----------------------|--------------------|---------|
| Mean Hb, g/dL – n (SD) | 5.02 (0.81)          | 5.43 (0.71)        | ns      |
| Mean MCV, fl – n (SD) | 85.4 (20.7)           | 88.4 (16.6)        | ns      |
| Microcytic – n (%)    | 42 (54.5)             | 2 (22.2)           | ns      |
| Normocytic – n (%)    | 14 (18.2)             | 5 (55.6)           | <0.05   |
| Macrocytic – n (%)    | 21 (27.3)             | 2 (22.2)           | ns      |
| Thrombocytopenia – n (%) | 14 (18.2)           | 2 (22.2)           | ns      |
| Leukopenia – n (%)    | 12 (15.6)             | 1 (11.1)           | ns      |
| Lymphopenia – n (%)   | 25 (32.5)             | 4 (44.4)           | ns      |

* a As compared with non-microcytic anemias.
* b As compared with microcytic anemias.
* c As compared with non-macrocytic anemias.

### Table 3 – Diagnosis Related Groups (DRG) according to International Classification of Diseases (ninth revision) Clinical Modification coding.

| DRG                  | Type | Number of cases |
|----------------------|------|-----------------|
| 12                   | MED  | 1               |
| 14                   | MED  | 1               |
| 122                  | MED  | 1               |
| 123                  | MED  | 1               |
| 135                  | MED  | 1               |
| 138                  | MED  | 1               |
| 142                  | MED  | 1               |
| 144                  | MED  | 1               |
| 172                  | MED  | 6               |
| 174                  | MED  | 8               |
| 179                  | MED  | 1               |
| 180                  | MED  | 1               |
| 182                  | MED  | 4               |
| 188                  | MED  | 1               |
| 189                  | MED  | 1               |
| 190                  | MED  | 1               |
| 239                  | MED  | 1               |
| 271                  | MED  | 1               |
| 304                  | SURG | 1               |
| 310                  | SURG | 1               |
| 316                  | MED  | 2               |
| 395                  | MED  | 31              |
|                      | • Iron deficiency anemia | 19              |
|                      | • Secondary or not specified anemia | 6              |
|                      | • Myelodysplasia | 2               |
|                      | • Pancytopenia | 2               |
|                      | • Megaloblastic anemia | 2              |
| 397                  | MED  | 2               |
| 403                  | MED  | 2               |
| 473                  | MED  | 1               |
| 570                  | SURG | 1               |
| 571                  | MED  | 1               |
| 574                  | MED  | 6               |
| 576                  | MED  | 4               |
| All                  |      | 85              |
The authors declare no conflicts of interest.

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