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Original article

Does this patient have cancer? The assessment of age, anemia, and erythrocyte sedimentation rate in cancer as a cause of weight loss A retrospective study based on a secondary care university hospital in Romania

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Abstract

Background: "Does this patient have cancer?" is a question frequently asked when confronted by patients with involuntary weight loss. The aim of this study was to assess the value of age, erythrocyte sedimentation rate (ESR), and anemia in the diagnosis of cancer as a cause of involuntary weight loss.
Methods: A retrospective study of 7850 patients admitted to the Department of Internal Medicine from January to September 2003 was performed. Especially selected were 431 patients with weight loss. Age, ESR, hemoglobin, and the discharge diagnosis were recorded.
Results: Twenty-four percent of the patients with involuntary weight loss had cancer. Age, ESR, and anemia were found not to be of value in the diagnosis of cancer (areas under the curve were 0.684, 0.690, and 0.766, respectively). When diagnostic tests for age, a high ESR, and anemia were used serially, the positive predictive value for a malignancy was 64% (CI: 27–90%); when the tests were utilized in parallel, the negative predictive value was 91% (CI: 85–100%).
Conclusions: Any patient admitted to our Department of Internal Medicine for involuntary weight loss had a 24% probability of having a malignancy. Neither age, nor ESR, nor anemia, used separately as a multilevel, diagnostic test or combined serially or in parallel, could exclude or rule in the diagnosis of cancer. However, they could increase (from 24% to 64%) or decrease (from 24% to 9%) the probability of cancer.

Keywords: Anemia; Cancer; Erythrocyte sedimentation rate; Predictive value of tests; Retrospective studies; Weight loss

1. Introduction

A serious illness like cancer is always suspected in patients with weight loss, a high erythrocyte sedimentation rate (ESR), or anemia. The question of how far we should proceed with more and more invasive and/or expensive investigations when facing this diagnostic problem remains unanswered.

A few studies have assessed weight loss, anemia, and ESR jointly as diagnostic tests and others have done so separately in different types of cancer [1–14], but none refers to cancer in a general way and none has calculated predictive values or likelihood ratios. Former studies on involuntary weight loss found that most patients with cancer had abnormalities at the clinical examination and/or routine blood tests. These studies established different diagnostic regression models including clinical and laboratory parameters as age, complete blood count, ESR, serum albumin,

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alkaline phosphatases, aminotransferases, gamma-glutamyl transpeptidase, and lactate dehydrogenase [15–17].

We chose to assess these three simple and largely utilized diagnostic tests (age, hemoglobin, and ESR) because they can be used in the diagnosis of any kind of cancer in general practice or in internal medicine.

2. Methods

The records of 7850 patients admitted to the Department of Internal Medicine of a secondary care university hospital from January to September 2003 were reviewed and the records of all patients with involuntary weight loss were selected for further study. Weight loss was defined as a loss of more than 5% of the initial weight [18] and it was among the three most important reasons for admission. For those records where exact data concerning weight loss were missing (unknown initial weight in 137 cases, 32%), the inclusion criterion was only the presence of weight loss among the three most important reasons for admission. Patients with known malignancy were excluded. Ultimately, the records of 431 patients with involuntary weight loss were included in the study.

Age, ESR, and hemoglobin were dichotomized with, as cut-off values, the closest values to the upper left-hand corner from their receiver operator characteristic (ROC) curves [19], which were 62 years for age, 29 mm/h for ESR, and 10 g/dl for hemoglobin (Hb).

The investigative work-up was not standardized. However, all of the patients had a blood cell count with ESR, essential biochemical tests, a chest radiograph, and abdominal ultrasonography. Depending on the clinical examination and these screening tests, more complex blood tests, endoscopic investigations, computed tomographies, and/or surgical interventions were performed. Cancer was always diagnosed by histopathology.

After leaving the hospital, the patients were not followed up (except for cases who were readmitted to the same department during the study period).

For the construction of a diagnostic model, we used multivariate analysis by logistic regression, in which the dependent variable was the presence of cancer as the cause of the weight loss and the independent variables were age, anemia, and ESR. The sample was randomly divided into a derivation set (225 patients; 6 did not enter the analysis because of missing data), on which the model was developed, and a validation set (206 patients; 6 also did not enter the analysis because of missing data), on which the model was tested. Once the model was validated, we reunited the split sample for the final model so that the larger sample size could give the final model tighter confidence intervals [20].

SPSS 10.0 software (SPSS, Inc., Chicago, IL., USA) was used for the database construction, ROC curves, and multivariate analysis, and CATmaker 1.1 (Centre for Evidence-Based Medicine, Oxford, GB, 2004) for the calculations related to the attributes of the diagnostic tests studied.

Table 1
Age used as a multilevel diagnostic test for cancer as a cause of weight loss

Age (years) (quartiles)	LR+[a]	PPV[b]
<46	0.37	11%
47–60	0.67	18%
61–70	1.55	33%
>71	1.85	37%

[a] Positive likelihood ratio.
[b] Positive predictive value for a cancer prevalence of 24%.

Table 2
ESR used as a multilevel diagnostic test for cancer as a cause of weight loss

ESR (mm/h) (quartiles)	LR+[a]	PPV[b]
<11	0.31	9%
11–23	0.76	19%
24–53	1.15	26%
>53	2.23	41%

[a] Positive likelihood ratio.
[b] Positive predictive value for a cancer prevalence of 24%.

3. Results

The causes of weight loss were: digestive diseases (except cancer) 137 cases (32%); chronic non-digestive diseases 99 (23%); psychiatric diseases and socioeconomic cause 53 (12%); infections 39 (9%); and cancer 104 cases (24%), including 22 patients (5%) with gastric cancer, 15 (3%) with colonic cancer, and 14 (3%) with pulmonary cancer.

The areas under the ROC curves for age, ESR, and hemoglobin were 0.684, 0.690, and 0.766, respectively.

The values of age, hemoglobin, and ESR, utilized separately as multilevel, diagnostic tests, are reported in Tables 1–3.

In multivariate analysis by logistic regression made on the derivation set of 219 patients, the equation of the diagnostic model was: LOGODDS (CANCER) = −2.501 + 0.956 (AGE > 62) + 0.88 × (ANEMIA) + 1.236 × (ESR > 29). Based on this equation, the estimated probabilities of cancer with their confidence intervals were calculated (Table 4, 4th

Table 3
Hemoglobin level used as a multilevel diagnostic test for cancer as a cause of weight loss

Hb (g/dl) (quartiles)	Patients with cancer	Patients without cancer	Total no. of patients	LR+[a]	PPV[b]
≥13.1	4	28	32	0.45	13%
12.1–13	4	144	148	0.09	3%
10.6–12	44	97	141	1.44	31%
<10.5	51	57	108	2.83	47%

[a] Positive likelihood ratio.
[b] Positive predictive value for a cancer prevalence of 24%.

Table 4
Involuntary weight loss: the probability of having cancer (logistic regression)

ESR>29 mm/h	Anemia (Hb<10 g)	Age>62 years	Cancer risk (estimated, derivation set) (% with 95% CI)	Cancer risk (observed, validation set) (%)	Number of patients in the validation set	Cancer risk (final model on the whole sample) (% with 95% CI)
No	No	No	7 (6–83)	7	70	9 (0–15)
Yes	No	No	22 (12–37)	27	26	18 (12–27)
No	Yes	No	16 (8–30)	13	8	19 (12–30)
No	No	Yes	15 (10–30)	27	48	23 (15–32)
Yes	Yes	No	40 (13–75)	50	10	36 (16–63)
Yes	No	Yes	42 (15–99)	30	24	41 (21–66)
No	Yes	Yes	34 (11–68)	100	1	43 (21–68)
Yes	Yes	Yes	64 (17–94)	70	13	64 (27–90)
			219 pts		200 pts	

column). These values were compared with the probabilities of cancer observed in the validation set (Table 4, 5th column). The final model (Table 5), whose equation is: LOGODDS (CANCER) = −2.36 + 1.150 × (AGE > 62) + 0.921 × (ANEMIA) + 0.861 × (ESR > 29) was developed on the whole sample and the estimated probabilities of cancer as the cause of the weight loss derived from this model are reported in Table 4 (6th column).

Estimated from this equation, the patient's probability of having a malignancy as the cause of his weight loss was equal to 9% if hemoglobin was ≥10 g/dl, ESR <30 mm/h, and age <63 years (equivalent to utilization of the tests in parallel [21]). The same risk was equal to 64% if hemoglobin was <10 g/dl, ESR >29 mm/h, and age >62 years (equivalent to serial utilization of the tests).

Thirty-two patients had anemia, a high ESR, and were older than 62 years simultaneously (the tests applied serially were positive). Among them, 20 had a malignancy and 12 were false-positives. For these 12 false-positives, the diagnoses at discharge were: pernicious anemia ($n=2$), hyperthyroidism ($n=2$), myelodysplasia ($n=2$), gastric and duodenal ulcer ($n=1$ each), cirrhosis of the liver ($n=1$), pneumonia + hepatic cirrhosis ($n=1$), medullary aplasia ($n=1$), and hypothyroidism (?) ($n=1$). The 20 true-positive patients had gastric cancer ($n=6$), colonic cancer ($n=4$), prostate cancer ($n=2$), prostate cancer with metastases ($n=1$), metastasis with unknown primary site ($n=2$), malignant lymphoma ($n=2$), esophageal cancer ($n=1$), thyroid cancer ($n=1$), and leukemia ($n=1$).

The false-negative rate for the tests applied in parallel was 9% (CI: 0–10%; patients without anemia, with a low ESR, and who were younger than 63 years who had a cancer). These patients had colonic cancer ($n=2$), ovarian cancer ($n=2$), gastric cancer ($n=1$), pulmonary cancer ($n=1$), hepatic cancer ($n=1$), suprarenalian cancer ($n=1$), testicular cancer ($n=1$), malignant lymphoma ($n=1$), and carcinoid syndrome ($n=1$) — in total 11 patients.

For a cut-off with the probability of cancer of 50% (anyone with a probability of cancer estimated by the multivariate model >50% is predicted to have cancer) [20], the accuracy of the model was 78%, the sensitivity 20%, and the specificity 96%.

Is it worth noting that there was a negligible degree of correlation between age and ESR (r Pearson coefficient = 0.124, $p=0.011$), so ESR probably needs no correction for age [1].

4. Discussion

In our study, a quarter of the patients with involuntary weight loss had cancer, which is similar to what has been found in other series [15,22]. The probability of having cancer as the cause of involuntary weight loss increased with age, the presence of anemia, and a high ESR. However, when used as diagnostic tests, one cannot rule in or, even more importantly, rule out a diagnosis of cancer (Table 4).

When these tests for age, a high ESR, and anemia were used serially [21], the positive predictive value for a malignancy was 64% (CI: 27–90%) while, when used in parallel, the negative predictive value was 91% (CI: 85–100%) (Table 4).

As the sensitivity rates were low, one cannot eliminate malignancy based on the negativity of these tests. Also, the

Table 5
Cancer as a cause of involuntary weight loss: multiple logistic regression

Variable	Coefficient	Standard error	p value	Odds ratio	Upper 95% confidence interval	Lower 95% confidence interval
Age>62 years	1.150	0.249	0.000004	3.157	1.937	5.146
Hemoglobin<10 g/dl	0.921	0.294	0.002	2.512	1.412	3.935
ESR>29 mm/h	0.861	0.260	0.001	2.366	1.423	3.935

Likelihood ratio test: $p=0.000001$; Hosmer–Lemeshow goodness-of-fit test: $p=0.782$.

false-negative rate was still important (9%) when the tests were used in parallel, whereas sensitivity grew to 87%, with a negative likelihood ratio of 0.17. However, when a patient was younger than 63 and had neither anemia nor a high ESR, his chance of having a malignancy was almost three times lower than before the application of these tests (pre-test probability=prevalence=24%, post-test probability=9%). In a primary care setting, where the prevalence of cancer is lower, these tests, applied in parallel, may be very useful in ruling out a malignancy.

Setting a cut-off value higher than 10 g/dl of hemoglobin for anemia would have increased the sensitivity and, therefore, the negative predictive value. As can be seen from Table 3, a hemoglobin value higher than 12 g/dl almost ruled out cancer; only 8 patients with neoplasia (1.86%) had such a value (two patients, one with liver and one with pulmonary cancer, had polyglobulia). The accuracy of anemia as a diagnostic test for cancer was diminished by the fact that many patients without cancer had anemia, due to other chronic diseases that eventually produced the weight loss or because of socio-economic factors.

This was a retrospective study without follow-up. Therefore, there are inherent bias, especially misclassification bias. Actually, patients who were not diagnosed with a malignancy may have had one diagnosed later. A future prospective study on a larger sample (to narrow the confidence intervals) and in a primary care setting would be welcome. Though simple and utilized daily, these tests have not yet been completely evaluated.

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