Involuntary weight loss without specific symptoms: a clinical prediction score for malignant neoplasm

J.L. HERNÁNDEZ, P. MATORRAS, J.A. RIANCHO and J. GONZÁLEZ-MACÍAS

From the Department of Internal Medicine, University Hospital Marqués de Valdecilla, University of Cantabria, Santander, Spain

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Summary

Background: Involuntary weight loss (IWL) is a non-specific symptom frequently found in the setting of a malignant neoplasm. There is no established diagnostic approach for patients presenting with isolated IWL, i.e. without data suggesting a particular organ involvement or system disorder.

Aim: To assess the clinical probability of cancer in patients with isolated IWL by means of a score based on simple clinical and laboratory parameters.

Design: Retrospective analysis, followed by prospective model validation.

Methods: We analysed data from 328 patients who were treated at our Internal Medicine Department because of isolated IWL from January 1991 to December 1997. A predictive model for cancer was developed and validated. For use in clinical practice, a prediction score was derived from the regression model.

Results: There were 236 in-patients (72%) and 92 out-patients (28%). Malignancies were the most frequent cause of isolated IWL (35%), followed by psychiatric disorders (24%). Age, white blood count, and serum albumin, alkaline phosphatase, and lactate dehydrogenase levels were selected as the best predictors. The regression model discriminated relatively well between patients with or without a malignant neoplasm (area under the ROC curve 0.90, 95%CI 0.88–0.92). Model sensitivity was 69%, specificity 93% and positive likelihood ratio 9.9 (using a cut-off point of 0.5).

Discussion: We believe this to be the first study to attempt a systematic approach to the diagnosis of isolated IWL. The approach, based on very simple clinical and laboratory data, should assist the physician in a rational approach to such patients.

Introduction

Involuntary weight loss (IWL) is a non-specific symptom that is very common in diseases with chronic or subacute courses. Together with asthenia, anorexia and malaise, it is often referred to as ‘constitutional symptoms’. Most frequently, IWL is accompanied by other more organ-specific manifestations that act as ‘key’ features for patient diagnosis, but this is not always the case. In the case of ‘isolated IWL’, differential diagnosis may be challenging.

Most causes of isolated IWL belong to one of three categories: malignant neoplastic diseases, chronic inflammatory/infectious diseases, or psychiatric disorders. Other common diseases are also possibilities, such as hyperthyroidism or diabetes. The most important diagnostic step when dealing with isolated IWL is usually to differentiate the first diagnostic category from the others.

There is no clearly established approach to the diagnosis of patients presenting with IWL. We studied a large unselected sample of such patients, to develop a method of identifying those with underlying malignant neoplastic disease.
Methods

Study population

We studied all in-patients and out-patients referred to the General Internal Medicine Department of our Hospital for isolated IWL from January 1991 to December 1996. Marqués de Valdecilla Hospital is a 1000-bed urban tertiary care teaching hospital in the north of Spain, to which patients are referred from a population of about 500,000 inhabitants. The decision for the patients to attend on an in-patient or out-patient basis was taken by their general practitioner or by the hospital Emergency Unit staff, without predefined guidelines.

For the purpose of the study, isolated IWL was defined as a weight loss of at least 5% of body weight in the last 6 months. The IWL was considered ‘isolated’ when it was not accompanied by any symptom or sign related to an organ or system, and the first set of diagnostic tests (see below) did not reveal any reliable diagnostic leads. If a cause for the isolated IWL was not found after 2 weeks of hospital study, or after two out-patient visits, it was labeled as ‘isolated IWL of unknown origin’. When the cause remained elusive after 6 months of intensive follow-up, the patient was considered to have a ‘isolated IWL of definitive unknown origin’. If a cause for the isolated IWL was identified, the syndrome was classified as ‘isolated IWL of known origin’.

The inclusion criteria were: (i) those contained in the IWL definition; (ii) lack of any clinical feature suggesting a particular organ problem or system disease; and (iii) non-significant results from the routine diagnostic tests at the Emergency Unit of our hospital: complete blood count (without erythrocyte sedimentation rate), serum basic biochemical profile (glucose, urea, creatinine, sodium and potassium), and chest and plain abdomen radiographs.

For weight loss to be accepted as fulfilling the required criteria, it should have been verified using scales. If the patients did not have a numerical verification of their weight loss, they were only included in the study if they met at least two of the three following criteria: evidence of change in clothes size, corroboration of the reported weight loss by a relative or friend, and ability to give a numerical estimate of such loss.7

Patients were excluded for any of the following reasons: (i) a previously known diagnosis of a disease that could explain the IWL syndrome (e.g. malignant neoplasm); (ii) any clinical, analytical or radiographic abnormality suggesting a particular diagnosis; (iii) weight loss was intentional; (iv) use of diuretics in the 3 months prior to presentation; (v) lack of clinical confidence in any of the data required to be included in the study.

Design

The study consisted of two parts. The first part (January 1991 to December 1994), retrospectively reviewed clinical charts of patients admitted to the General Internal Medicine Department or referred to its out-patient clinic with a preliminary diagnosis of IWL. Follow-up was by means of clinical charts, mail or telephone contact. Personal re-evaluation of the patients at least 12 months after diagnosis was possible in 95% of cases.

The second part (January 1995 to December 1996) was prospective. Patients admitted to the General Internal Medicine Department and new patients attending its out-patient clinic were reviewed on a daily basis by one of the authors (JLH). If additionally there were no other orientating symptoms or signs, and no relevant alterations in the complete blood count, serum elemental biochemical profile, or chest and plain abdomen radiographs, they were considered as having isolated IWL, and included in the study. A standardized set of analytical and radiological studies (see later) was then performed. The remainder of the diagnostic evaluation was left to the clinician in charge of the patient. If after 2 weeks evaluation or two out-patient visits an aetiological diagnosis was not reached, patients were labeled as ‘isolated IWL of unknown origin’. When a diagnosis was in fact made, medical records were reviewed 6 months later to be sure the diagnosis had not changed. They were reviewed again at the end of the study period (December 1997) to obtain survival data. Patients with isolated IWL of unknown origin were evaluated at 3, 6 and 12 months. In these follow-up visits, complementary studies were requested as necessary, according to the symptoms or signs present.

Data collection

The following data were collected for each patient: age, sex, out- or in-patient condition, degree of weight loss, smoking habit, alcohol consumption, drug use, final diagnosis (malignant neoplasm or non-malignant disease), haemoglobin level, white blood cell count, platelet count, erythrocyte sedimentation rate, serum glucose, urea, creatinine, uric acid, sodium, potassium, calcium, cholesterol, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase, and lactic dehydrogenase levels, serum protein electrophoresis, urinalysis
and thyroid hormone levels (TSH and free T4 – FT4-).

Other tests relevant to the diagnosis of isolated IWL were also recorded in particular cases, depending on whether the clinicians in charge of the patients had requested them. That was the case with tumour markers (CEA, CA-19.9, CA-125, AFP, CA-15.3, PSA), antinuclear antibodies, rheumatoid factor, imaging techniques findings (radiographs, ultrasounds, computed tomographies, endoscopies, scintigraphies) and pathological studies.

**Diagnoses**

For a patient to be considered as having isolated IWL of unknown origin, diagnosis of a disorder that could produce IWL had to be ruled out. A disease was accepted as being responsible for the IWL when it is recognized in the medical literature as a cause for it, and when its treatment resulted in an improvement of the syndrome, or if the IWL and the underlying disease ran parallel courses. For further analysis, diseases identified as causes of isolated IWLs were classified according to the International Classification of Diseases, 9th revision, clinical modification (ICD-9, CM), with three-digit codes. Diagnostic assignment was performed independently by two of the authors. Disagreements (<5%) were resolved by consensus.

**Statistical analysis**

All statistical calculations used SPSS and GraphRoc 2.0 software. Continuous variables are expressed as the arithmetic mean ± SD, and were compared by the two-tailed Student’s t-test or Mann-Whitney U-test, as appropriate. Discrete variables were compared using the χ² test.

The association between clinical or analytical data and the presence of a malignant neoplasm was first estimated by univariate logistic regression analysis. The cut-points of the variables were chosen according to the normal limits of our laboratory, or using clinical guidelines to simplify the score calculation. All the variables statistically associated with the presence of malignant neoplasm were entered into a stepwise multivariate analysis. The predicted probability of neoplasm was calculated from the regression model for each patient. The reliability of the model was evaluated using the Hosmer-Lemeshow goodness-of-fit test. The area under the ROC curve and its 95% CI tested the discriminative ability of the regression model. This model was constructed using data from the patients enrolled from 1991 to 1995 (derivation set), and then validated in the group of patients included in the last year (1996) of study (validation set).

To enable the use of the regression model in clinical practice, a prediction rule was developed to forecast malignant neoplasm in the setting of an isolated IWL. In the prediction rule, a score was assigned to the level of presence of each clinical characteristic, based on regression coefficients. These scores were added into a sum score that, through the logistic formula, corresponded with a predicted probability of malignant neoplasm. Based on a clinical pretest probability for malignant neoplasm, and the likelihood ratio obtained with the application of the score system, a post-test probability was calculated using the conventional formulas for odds calculations. The clinical usefulness of a diagnostic test is largely determined by the accuracy with which it identifies its target disorder, and the accuracy measure we focused on is the likelihood ratio, which represents the probability of a given test result among people with a disease, divided by the probability of that test result among people without the disease. The formal use of likelihood ratios requires converting pre-test probabilities to odds, according to this equation: pre-test probability/(1–pre-test probability). Once you have the pre-test odds, the post-test odds can be calculated by multiplying the pre-test odds by the likelihood ratio. The post-test odds can be converted back into probabilities using a formula of post-test probability = odds post-test/odds post-test + 1). These calculations, based on Bayes’ theorem, can be greatly simplified using the nomogram proposed by Fagan.

**Results**

Overall 35 402 patients attended our General Internal Medicine Department during the study period. The total number of patients presenting with an IWL was 1211 (3.4% of all patients attended). The criteria for isolated IWL were fulfilled by 358 (29.5% of IWL patients). Sixty-seven (19%) were considered as having isolated IWL of unknown origin. At the end of the study, only 20 could be classified as isolated IWL of definitive unknown origin. Thirty others were lost to follow-up. Therefore, 308 were available to study the relationship between the clinical and analytical data and the presence or absence of a neoplasm.

The mean age of the isolated IWL patients was 65 ± 17 years (range 15–97). Out-patients were significantly younger than in-patients (54 ± 20 vs. 70 ± 12 years, p < 0.01). Some 52% of the isolated IWL patients were males (41% of out-patients, 56% of in-patients).

The time elapsed from symptom onset to medical evaluation was nearly 3 months. Mean weight prior
to weight loss was 63 ± 5 kg. The mean percentage of weight loss was 8%. Thirteen patients were receiving diuretics; however, they had been started on them long before the beginning of the IWL, and therefore they were not excluded from the study.

Of the 308 patients for whom a final diagnosis was established, 115 had a malignant neoplasm, 113 an organic non-malignant disease, and 80 a psychiatric disorder (Table 1). Other characteristics of part of this series have been previously published.16

**Model development**

Table 2 shows the association between clinical and analytical data and the presence of a neoplasm.
(73 ± 9 vs. 61 ± 18, p < 0.001), were more often male, and had more pronounced weight loss. They more often presented with anaemia, and had higher ESR (57 ± 40 vs. 31 ± 33), higher liver enzyme levels, and lower serum concentrations of albumin, cholesterol and albumin corrected calcium. No other significant differences were found.

The results of multivariate analysis are shown in Table 3. When the above variables were entered into the multivariate analysis, the strongest predictors of a malignant neoplasm in the setting of an isolated IWL were: age > 80 years (p = 0.016), white blood cell count > 12 × 10^9/mm^3 (p < 0.0001), serum albumin concentration < 3.5 g/dl (p < 0.0001), serum alkaline phosphatase level > 300 U/l (p < 0.00001), and serum lactate dehydrogenase level > 500 U/l (p < 0.00001). The multivariate logistic regression model can be written as:

\[
\text{Probability of malignant neoplasm} = \frac{1}{1 + e^{-LP}}
\]

where linear predictor \( LP = -0.91 + (1.23 \times \text{age}) + (1.27 \times \text{white blood cell count}) - (1.87 \times \text{serum albumin concentration}) + (2.48 \times \text{serum alkaline phosphatase level}) + (2.53 \times \text{serum lactate dehydrogenase level}) \).

Plausible interactions were tested, including age, sex, smoking habits and alcohol abuse, but they were not significant or did not improve the model.

Figure 1 shows the ROC curve generated by these predictors. The area under the curve was 0.90 (95% CI 0.88–0.92). Given a cut-off point of 0.5, sensitivity was 0.69 and specificity 0.93. The positive and negative predictive values were 0.83 and 0.85, respectively, and the likelihood ratio of a positive result 9.9. The model allowed the correct classification of 85% of the patients (93% of those with non-malignant disorders, and nearly 70% with malignant diseases). Sensitivity increased as the considered cut-off point decreased. For example, at a cut point of 0.2, sensitivity was 91%, specificity 67%, positive predictive value 59%, negative predictive value 93%, and likelihood ratio of a positive result, 3.

The model incorrectly classified 27 patients with malignancies (cut-off point of 0.5). Of these, 16 cases were gastric and pancreatic neoplasms.

These clinical and laboratory variables were used to construct a prediction rule for the presence of a malignant neoplasm in the setting of an isolated IWL. A scoring system was developed by assigning points to each predictor according to a simple modification of the logistic coefficients (Table 4). Patients’ total scores ranged from 2 to 7. The probability associated with this value was derived from the formula \( p = 1/(1 + e^{-LP}) \). In the setting of an isolated IWL, a score < 0 indicates a low probability for a malignant neoplasm (p = 0.0–0.30); a score from 0 to 1, an intermediate probability (p = 0.30–0.60); and a score > 1, a high probability for a malignant neoplasm (p > 0.60).

Using the 0 and 1 cut-off points of the score, and taking into account the number of patients in each of the three resulting intervals (< 0, 0–1, > 1) along with the diagnosis of malignant or non-malignant disease, the likelihood ratios can also be calculated (Table 5).

### Model validation

The model and the score system were validated in the group of patients recruited in the last year of the study (validation set, \( n = 52 \)). The area under the ROC curve (Figure 1) in this group of patients was 0.89 (95% CI 0.87–0.91). Given a cut-off point of 0.50, sensitivity was 0.72 and specificity 0.81. The negative and positive predicted values were 0.81 and 0.73, respectively.
Discussion

Our objective was to develop a prediction model for cancer in the setting of an isolated IWL, using simple clinical and laboratory data. The model allowed the correct classification of 85% of the patients (93% with non-malignant disorders, and 70% with malignant diseases). The negative predictive value of the model was 85%. The variables included are commonly used, and their measurement does not require invasive or expensive procedures. Because the use of mathematical formulae may be impractical in daily clinical practice, a score system has been derived, and the associated likelihood ratios for three different intervals have also been calculated. To our knowledge, no comparable data exist in the medical literature that allows the estimation of malignant disease prevalence in patients with isolated IWL. Although the sensitivity of the model is low when it is interpreted just as a dichotomous result (i.e. cancer probability higher or lower than 50%), we feel it provides useful information and helps to tailor the diagnostic work-up, when properly interpreted according to the stratified score results and the clinical characteristics of the patient.

In this study, the prevalence of malignant disease as a cause of isolated IWL was 37%. Therefore, that was the overall pre-test probability when facing a patient of this type. However, in clinical practice, the pre-test probability assigned to a particular patient may differ from that figure. For instance, a young woman presenting with insidious asthenia, predominantly in the morning, mild anorexia and slight weight loss, could probably be assigned a lower value (i.e. 5%). By contrast, an elderly man with marked asthenia that increases throughout the day and pronounced weight loss would surely be considered to have a higher pre-test probability of cancer (i.e. 80%). Table 6 shows three hypothetical case scenarios with different pre-test probabilities, and indicates how the initial probabilities are modified depending on the results of the model here proposed.

Those estimations are based on Bayes’ theorem, which allows to the estimation of post-test probability of a given disease, by taking into consideration pre-test probability and the likelihood ratio of the test result. This approach also permits the stratification of test results into different intervals, thus obtaining more useful information than simply classifying the results as ‘positive’ or ‘negative’.

Likelihood ratios values >1 increase the probability that cancer is present, and the higher the likelihood ratio, the greater this increase. Conversely, values < 1 decrease the probability of malignant neoplasm, and the smaller the likelihood ratio, the greater the decrease in cancer probability. Thus, if the result of combining the likelihood ratio of the test result and pre-test probability of a particular patient leads us to a high post-test probability, the clinician should consider to pursue further the search for an occult neoplasm. However, if the post-test probability is low, such procedures could be avoided and the patient followed-up.

Although its sensitivity is low in a clinical sense, the model provides an useful additional tool in order to predict the probability of malignancy in patients presenting with IWL without specific symptoms. The usefulness of the proposed score is clear in the subgroups of patients with a score < 0 or > 1, who represent about 70% of the whole sample. The likelihood ratios associated with those values are 0.07 and 28, respectively. A likelihood ratio
>10 or < 0.1 generates large and often conclusive changes from pre-test to post-test probabilities.\(^{17}\) For the remaining 30% of patients with a score between 0 and 1, the model only slightly modifies pre-test probability and thus does not provide substantial additional information.

Analysis of the malignancies incorrectly classified by the model revealed that most of them (16/27) were gastric and pancreatic neoplasms. Further studies are needed to evaluate whether the addition of serum CA 19.9 levels, and standard barium examination, or endoscopic procedures of the gastroduodenal tract, could improve the clinical usefulness of this model.

Our study has some limitations. First, the model was developed in a retrospectively studied series of patients, although it has been prospectively validated. This suggests caution until tested in new studies. Second, the possibility that its utility changes with the populations in which the model is used (e.g. for geographical or ethnic reasons), may not be discounted. Third, it is unclear to what extent the results can be extrapolated to other population groups with different prevalences (and thus, different predictive values) of malignant tumour. Nevertheless, other studies in our country found similar results in the prevalence of cancer among patients with IWL.\(^{18}\)

To conclude, we believe this to be the first study addressing the issue of a systematic approach to the diagnosis of patients with IWL without accompanying specific manifestations (which could be considered a counterpart to ‘fever of unknown origin’). The approach is based on very simple clinical and laboratory data and helps to establish the probability that a patient with isolated IWL has malignant disease.

References