Applied Medical Informatics
Original Research Vol. 43, No. 1/2021, pp: 14-23

Information-Theoretical Analysis of Blood Biomarkers for Age-Related Hip Fracture Risk Evaluation

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Received: October 13, 2020 /Accepted: January 17, 2021/ Published online: (February 1, 2021)

Abstract
Aim: Hip fractures are highly frequent and severe problem, increasing incidence and severity with aging and high disability and mortality rates. Hence, the ability to predict this condition can be of high value for preventive healthcare. The present work explores clinical biomarkers' application for hip fracture risk evaluation and prediction, using an information-theoretical methodology. *Material and Method*: A dataset on geriatric patients, with and without hip fracture, was analyzed, including blood biomarkers routinely available to physicians: albumin, urea, hemoglobin, calcium, and white blood cells. This research comprised geriatric patients hospitalized at the Shmuel Harofe Geriatric Medical Center, Israel. The patients' data, collected during 2012-2017, were accessed retrospectively. Normalized mutual information was utilized to establish correlations between the parameters, and the nearest neighbor rule with the weighted Hamming distance was used for the construction of a diagnostic decision rule for hip fracture risk evaluation. *Results*: We developed an algorithm (decision tree) for hip fracture risk group attribution for subjects under 80 years old. The algorithm provided the sensitivity of 0.581 with the 95% confidence interval (0.505, 0.653), and specificity of 0.540 with the 95% confidence interval (0.479, 0.604). This performance was comparable with the results of other common methods for hip fracture risk evaluation, yet the present method may be preferable in terms of data accessibility and the ability to determine the possible time of the fracture. *Conclusion*: The use of this method has been piloted in the clinic, and with further development and application, can help evaluate the risks of hip fracture in older subjects (aged 60 years or over) to optimize preventive interventions.

Keywords: Hip fracture; Diagnostic rule; Risk prediction; Geriatric patients; Information theory

Introduction

Hip fractures (breakage of the hip joint) are a highly frequent and severe geriatric population problem. The incidence of hip fractures in the US was estimated at about 1,000 per 100,000 in women and up to 500 per 100,000 in men. With aging, the incidence increases dramatically. In patients over 80, the incidence can reach up to 2000 in men and 3,000 in women per 100,000 subjects. The mortality from this condition is also very high. About 30% of people with a hip fracture will die in

the following year [1]. The majority of the subjects will experience severe functional disability [1]. The costs of treatment of this condition are also very high. Thus, in the US, a typical patient with a hip fracture will spend US $40,000 in the first year after hip fracture for direct medical costs and almost $5,000 in the years after that [1]. Notably, hip fracture is not a stand-alone condition but manifests and can result from various other age-related co-morbidities and associated conditions, such as osteoporosis, sarcopenia, reduced vision or mobility, balance problems, additional age-related diseases (cancer, neurodegenerative diseases, heart disease) and more [2]. Thus, clearly, the ability to mitigate this condition by early detection and prediction to enable early preventive intervention can have enormous medical and economic significance. Prevention necessitates the search for effective and convenient methods of hip fracture risk evaluation.

Several methods exist to evaluate risks for hip fractures. The most commonly used tools include the FRAX and Garvan fracture risk calculators. These calculators have high specificity and low sensitivity and utilize many input parameters, including parameters that necessitate special dosimetry equipment and sometimes uncertain premises (such as family history) [3,4]. Moreover, these methods do not indicate the age of the patient at risk of hip fracture. Our study aimed to overcome these drawbacks and create an algorithm for hip fracture risk attribution under the age of 80 years old, that is to say, at a relatively younger generation. This study aimed to develop an algorithm with a sufficiently high sensitivity to utilize information readily available to physicians.

Material and Method

In pursuing the proposed aim, we chiefly rely on a theoretically grounded, information-theory-based approach to address yet another common drawback in the construction of diagnostic rules, namely the reliance on heuristic methods without a theoretical substantiation [5-10].

Data Analysis and Algorithm

In the present work, the chosen information-theoretical measure of association of diagnostic parameters with the age of hip fracture occurrence is the normalized mutual information (NMI), which is also termed "uncertainty coefficient". In contrast to the evaluation of parameters' correlations using the linear correlation coefficient, the normalized mutual information enables the investigators to determine non-linear association of the diagnostic evaluation parameters of interest with the presence of disease. Moreover, normalized mutual information value provides the exact amount of information (or informative value) that each diagnostic parameter contains about the presence of hip fracture at a particular age.

We calculate the normalized mutual information according to the standard procedure. Thus, we assume X to be a discrete random value having the following distribution function

X	x_1	x_2	.....	x_n
P	p_1	p_2	.....	p_n

where X can be any diagnostic evaluation parameter of interest, n is the number of categories of the evaluation parameter, p_i designates the frequency of the category x_i. The formula presented in Eq(1) determines the Entropy of a random value X [11,12]:

$$H(X) = -\sum_{i=1}^{n} p_i \log p_i \qquad (1)$$

We assume X and Y to be discrete random values (evaluation parameters). In the present case, X signifies markers of the disease, whereas Y signifies indicators of the disease (presence or absence). The algorithms for the calculation of normalized mutual information between parameters or parameter combinations have been described earlier [5,6,10]. Here, we build on these methods to create a new information-theory-based methodology for risk group attribution for hip fractures.

In short, for the parameters X and Y, the value of normalized mutual information *C* is calculated by the standard formula [11,12]:

$$C(X,Y) = \frac{I(X;Y)}{H(Y)} = \frac{H(X)+H(Y)-H(XY)}{H(Y)} \qquad (2)$$

where H(X), H(Y), H(X,Y) are, respectively, the entropies of random values X, Y, and X×Y. The normalized mutual information approaching zero signifies a weaker correlation value, whereas the normalized mutual information approaching unity shows a stronger correlation between evaluation parameters [11,12].

It is important to emphasize that normalized mutual information measures the precise amount of information that each evaluation parameter contains about the presence of a hip fracture. Based on such exact quantities of information or informative weights/values of all the parameters, it is possible to create a diagnostic rule to evaluate the person's risk to develop hip fracture at a particular age, categorizing the subjects into risk groups according to the strength of the correlation. In constructing the algorithm for risk group categorization, we do not use the common heuristic methods such as logistic regression, neural networks, or deep learning [13]. When applying mathematics in medicine, we believe that the use of heuristic approaches (algorithms) should be possibly avoided as theoretically unsubstantiated. Rather, we use the theoretically-grounded method of information theory.

As an algorithm for assigning a patient to a risk group, we used the nearest neighbor rule with the weighted Hamming distance [7,14,15]:

$$d(v,z) = \sum_{j=1}^{n} 2^{j-1} \left| v_j - z_j \right| \qquad (3)$$

where $v=(v_1, v_2,\ldots, v_n)$ and $z=(z_1, z_2,\ldots,z_n)$ are n-dimensional binary vectors, and the weights $2^0, 2^1, \ldots, 2^{n-1}$ are defined by the corresponding normalized mutual information.

Under the present approach, the initial parameters are transformed into binary parameters, while each pattern is a set of n-dimensional binary vectors. For each parameter, the normalized mutual information estimates the correlation of this parameter with hip fracture. Thus, the more the normalized mutual information, the greater is the correlation and the greater is the weight this parameter obtains in the weighted Hamming distance. The attribution to the risk group is determined by the vector $w=(w_1, w_1,\ldots, w_n)$ of patterns, found at the minimal distance from the vector $z=(z_1, z_2,\ldots,z_n)$ of the corresponding tested patient. That is to say, if the vector *w,* such that

$$d(w,z) = \min d(v,z) = \min \sum_{j=1}^{n} 2^{j-1} \left| v_j - z_j \right| \qquad (4)$$

where the minimum is searched on the set of all the vectors $v=(v_1, v_2,\ldots, v_n)$ of two patterns, belongs to the pattern 1, then the vector $z=(z_1, z_2,\ldots,z_n)$ is attributed to the group of patients corresponding to the pattern 1. And if it belongs to the pattern 2, then also the vector $z=(z_1, z_2,\ldots,z_n)$ belongs to the group of patients corresponding to the pattern 2.

The nearest neighbor rule's theoretical justification with the weighted Hamming distance was presented earlier [7,15]. To illustrate the rule, and facilitate its use in the clinic, we present this rule as a decision tree [16]. The application and algorithm for the construction of decision trees and analogous approaches have been presented earlier [7,8,17]. The approach described in [8] and used in this work is presented in the monograph [9]. Here we build on these methodologies to create a new method for risk group attribution for hip fractures.

The decision tree can be useful in clinical evaluation practice, mainly for two reasons: A decision tree diagnostic model closely follows the description of clinical decision making, and it can be easily theoretically justified and interpreted. In the present work, we built the decision rule regarding the risk of hip fracture for subjects under 80 years old, compared to subjects 80 years old and older, using a small set of diagnostic parameters routinely available to treating physicians. This way, we were able to demonstrate the potential common applicability of information-theoretical methodology to assess the risk of hip fracture.

It should be emphasized that all the data must be discretized for the application of the information-theoretical model. Here, the discretization thresholds (boundaries) were determined according to the algorithm for physiological boundaries evaluation by maximizing normalized mutual information [18]. Following the data discretization and calculation of the normalized mutual information values for all the parameters under consideration, we select the most informative parameters with the highest values of normalized mutual information for the diagnostic model construction. With these most informative parameters, we construct the diagnostic model using the weighted Hamming distance.

Case Materials

This research comprised geriatric patients hospitalized at the Shmuel Harofe Geriatric Medical Center in Beer Yaakov, Israel. The patients' data were accessed retrospectively, according to the principles of the Declaration of Helsinki. The Institutional Review Board at the Shmuel Harofe Geriatric Medical Center approved the study (IRB Approval No. 53, date of approval: 13/07/2017). The patient data used in this research were anonymized before the study.

The study included geriatric hip fracture patients consecutively admitted to a geriatric post-acute rehabilitation ward from nearby orthopedic departments during 2012-2017. All hip fracture patients suffered a traumatic low-energy pertrochanteric (extra-capsular) or sub-capital (intra-capsular) hip fracture, have undergone fracture fixation, were allowed full weight-bearing and were in a stable medical condition. As an additional control, a group of geriatric patients was included who were hospitalized in this period in the medical center due to functional decline following brain damage or prolonged hospitalization in a general hospital, yet without hip fractures. We excluded patients with other severe disabilities, for example, multiple traumas and medical conditions that would preclude active rehabilitation (e.g., severe chronic lung disease requiring constant oxygenation, cardiac failure in the functional capacity stage III-IV of NYHA) and transition to acute care departments due to severe complications. The patients were aged 64-103 years old. Complete medical details were extracted from each patient's medical chart retrospectively.

For the illustration of the proposed methodology, we selected a group of diagnostic evaluation parameters commonly available to treating physicians, mainly obtained from routine blood tests. The parameters represented different types of blood biomarkers, including cellular and/or immunological parameters (numbers of white blood cells, lymphocytes, and neutrophils), microelement levels (Calcium – Ca, Potassium – K, Sodium - Na), hematological parameters (hemoglobin, number of platelets), common metabolites (glucose, total cholesterol, urea, albumin, total protein, triglycerides, folic acid), enzymes (creatinine, alkaline phosphatase – ALP), physiological indicators (heart rate, systolic blood pressure, diastolic blood pressure), and a few selected medical conditions (Ischemic Heart Disease, Hyperliplidemia). For the construction of the diagnostic model, we used the data gathered at the patient's admission to the hospital, rather than at the discharge, to exclude the intervention's effects (rehabilitation). Gender was also included as an indispensable distinguishing parameter. Thus, altogether 23 diagnostic parameters were evaluated, from which the most informative parameters were selected for the construction of the diagnostic model. At a particular age range (below 80 years old vs. at 80+ years old), the risk of hip fractures was considered the diagnosed/predicted outcome. The markers' values equal to or above the boundary were designated as 1 for the algorithm construction and represented in red in the decision tree. A blue line was used for those with values below the boundary. Male subjects were designated as 0 or blue, and females as 1 or red. The presence of particular medical conditions (e.g., Hyperlipidemia, Ischemic Heart Disease) was coded as 1, the absence of those conditions as 0. Proceeding along the decision tree lines, we establish the presence of the diagnosed/predicted value, namely the occurrence of hip fracture below age 80 (R, Risk of an earlier hip fracture) vs. 80+ (N, No risk). The most informative parameters, those with the highest values of normalized mutual information, were selected for the construction of the decision tree to attribute patients to the risk group for the presence of hip fracture under 80 years of age.

Results and Discussion

We analyzed a total of 594 geriatric patients, including 372 patients with a hip fracture and 222 without a hip fracture. Among them, 367 were females and 227 males. The patients with a hip fracture included 242 females and 130 males. Moreover, 119 patients were younger than 80 years old, and 253 were 80 years old and older. Furthermore, to test the obtained decision rule for the hip fracture risk group attribution, we used an additional group of patients without a hip fracture, including 125 females and 97 males. Among them, 82 patients were younger than 80 years old, and 140 patients were 80 years old and older.

Table 1 shows the values of normalized mutual information (NMI, or the amount of information about the presence of hip fracture) for all the parameters in descending order. Table 1 also shows the boundaries according to which the parameters' binarization was performed. The parameters found to be most informative were: Albumin, Urea, Hemoglobin (Hb), Calcium (Ca), Gender and White Blood Cells (WBC). All above-mentioned parameters were included in the decision tree.

Table 1. Values of normalized mutual information (NMI) between particular diagnostic parameters and the presence of hip fracture under age 80 (the diagnosed parameter) vs. 80+. The Table also shows the boundary values for the particular parameters for the decision tree construction

	Parameter	Boundary	NMI
1	Albumin	3.31 g/dL	0.09587
2	Urea	42 mg/dL	0.06333
3	Hemoglobin	10.4 g/dL	0.04806
4	Ca	9 mg/dL	0.02723
5	Gender	1/0	0.01983
6	White Blood Cells	8500 1/μL	0.01832
7	Triglycerides	128 mg/dL	0.01719
8	Total protein	5.98 g/dL	0.01252
9	Diastolic Blood Pressure	66.5 mmHg	0.01252
10	Neutrophils	5500 1/μL	0.01207
11	Platelets	320000 1/μL	0.00893
12	Na	139 nmol/L	0.00827
13	Lymphocytes	1700 1/μL	0.00610
14	Creatinine	0.8 mg/dL	0.00283
15	Alkaline Phosphatase	90 U/L	0.00255
16	Total Cholesterol	160 mg/dL	0.00137
17	Ischemic Heart Disease	1/0	0.00119
18	Systolic Blood Pressure	127 mmHg	0.00080
19	K	4.3 nmol/L	0.00080
20	Heart Rate	77 BPM	0.00080
21	Blood Glucose	120 mg/dL	0.00071
22	Hyperlipidemia	1/0	0.00071
23	Folic Acid	8.5 ng/ml	0.00054

Figure 1 demonstrates the decision-making process, proceeding from the most informative (discriminative) parameter to the less informative parameters. Namely, the decision making proceeds from the most informative indicator Albumin (NMI=0.09587) to Urea (NMI=0.06333) to Hemoglobin (NMI=0.04806) to Calcium (NMI=0.02723) to Gender (NMI=0.01983) to the least informative in this group White Blood Cells (NMI=0.01832). This may roughly reflect the clinical decision-making process, first discerning the most salient diagnostic features and then fine-tuning the decision by the more nuanced parameters. Any number of available diagnostic parameters could be included in the diagnostic rule (decision tree), but the most discriminating features may be sufficient for practical purposes.

The findings of the most informative parameters are not surprising. Alterations in all these parameters were associated with frailty and aging states in earlier research [19]. Specifically, the

present work found the most informative parameter to be Albumin, the most abundant blood transport protein. In the past, albumin decrease has been associated with frailty and degenerative aging states in various studies [20,21] and with poor hip fracture outcomes in particular [22-24].

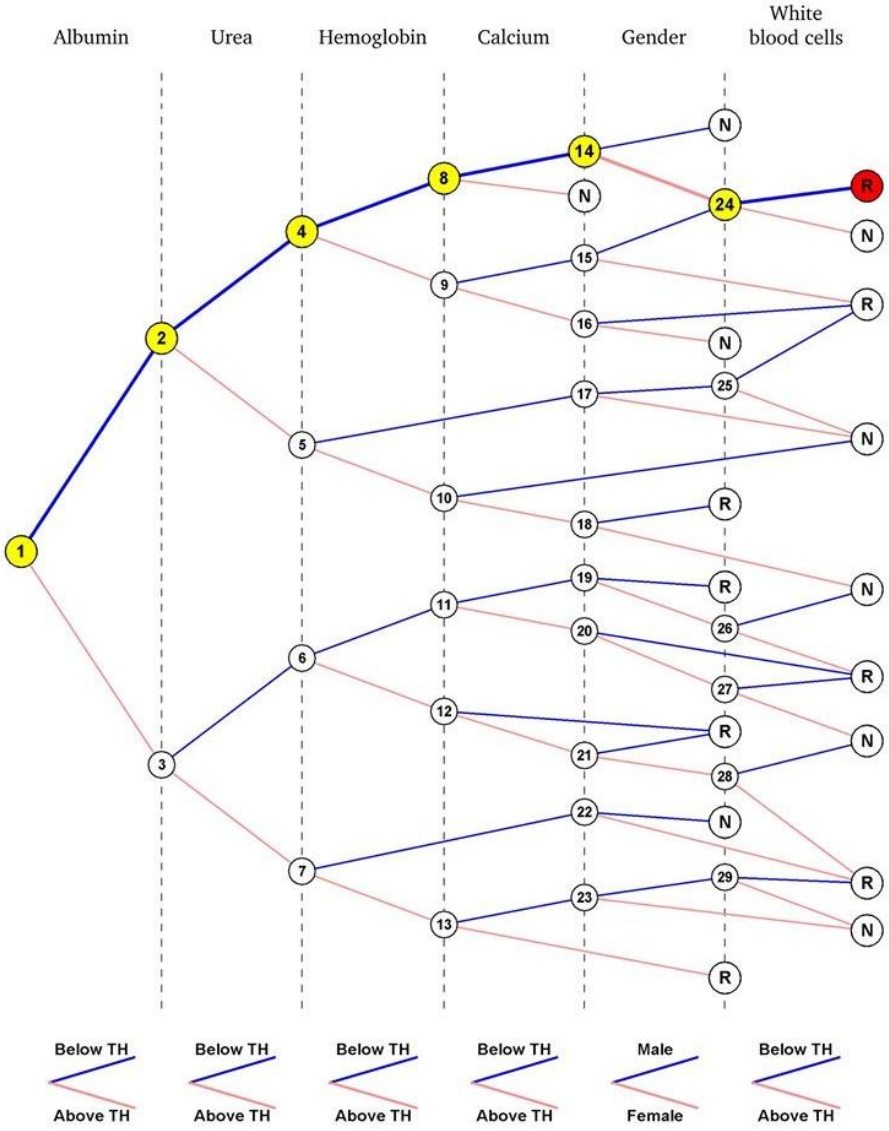

Figure 1. The decision rule for the evaluation of hip fracture under age 80 (code R, the diagnosed parameter, i.e. Risk of hip fracture under age 80) vs. 80+ (code N, i.e. No risk of hip fracture under age 80). According to the particular parameter values, the decision is made via proceeding along with the decision tree nodes below or equal and above the particular threshold - TH (Table 1).

Also, the high informative value of urea could indicate the high importance of protein metabolism and protein homeostasis in aging [25]. Furthermore, hemoglobin could give a special indication for the organisms' oxygen supply state [26], calcium for the state of the muscular and skeletal systems [27,28] and WBC for the immunological state [29]. The interrelation of the various parameters of those systems created the decision rule. Also, gender has been a well recognized discriminating parameter for frailty status, other aging-related conditions, and life expectancy [30,31]. Altogether, these parameters provided a substantial basis to create the decision rule.

Consider an example of the use of the decision rule (Figure 1). Consider a woman aged 68 (red-coded), with the following blood test parameters: Albumin=2.91, Urea=38.6, Hemoglobin (Hb)=9.7, Calcium (Ca)=8.09, White Blood Cells (WBC)=8100. Comparing these values with the values of boundaries for each parameter (Table 1), and coding accordingly as the blue line below the boundary

and red line equal and above the boundary, we obtain the following parameter value codes: Albumin (blue), Urea (blue), Hemoglobin (Hb) (blue), Calcium (Ca) (blue), Gender (red), White Blood Cells (WBC) (blue). With these parameter value codes, we proceed along with the nodes: 1-2-4-8-14-24, eventually arriving in the final node R (indicating hip fracture Risk below the age of 80, the diagnosed parameter). Such an example is typical. In women, hip fractures are more frequent than in men, and the relatively lower values of the majority of these parameters (below the threshold), especially for albumin, hemoglobin, and calcium, have been associated with frail states [19]. Yet it should be noted that also when the values for particular parameters are above the threshold (e.g., for albumin), it is possible to be categorized as having a risk of hip fracture at a younger age. This may illustrate the need to consider several diagnostic parameters simultaneously, as any parameter considered only individually may be misleading [10,32,33].

The decision rule produced satisfactory diagnostic results. Within the entire cohort of 372 patients with a hip fracture that was analyzed, 119 were younger than 80 years old, and 253 were 80 years old and older. The decision rule (decision tree) was constructed based on 34 patients younger than 80 and 39 patients 80 years old and older, having a hip fracture. The accuracy of the decision tree was tested. Testing was done on 299 patients having a hip fracture, under the study inclusion criteria, including 85 patients younger than 80 years old and 214 patients 80 years old and older, and also 222 patients who did not have a hip fracture, including 82 patients younger than 80 years old and 140 patients 80 years old and older. Among the 167 patients younger than 80 years old (with and without a hip fracture), the prediction was made correctly for 53+44=97 patients (53 – with the fracture, 44 – without the fracture). That is, the sensitivity was (97/167)≈0.581 with the 95% confidence interval (0.505, 0.653). Among the 354 patients 80 years old and older (with and without a hip fracture), the prediction was done correctly for 10+103+78=191 patients (10 - prediction of fracture before 80 y.o., 103 - prediction of fracture for 80 y.o. and older, 78 - no hip fracture). That is, the specificity was (191/354)≈0.540 with a 95% confidence interval (0.479, 0.604). Of the total number of patients 167+354=521, the prediction was done correctly for 97+191=288 patients. That is, the accuracy of the prediction was (288/521)≈0.553 with a 95% confidence interval (0.510, 0.595).

For the present purposes, the most important parameter is the sensitivity of the prediction, that is to say, the ability to correctly identify subjects below 80 years of age who are at risk of a hip fracture. The algorithm's sensitivity was 58.1%. That is to say, when validating the algorithm, within the group of patients that the algorithm suggested had an increased risk of hip fracture under 80 years old, almost 60% indeed had a hip fracture. Insofar as the sensitivity (the ability to correctly identify the risk group) is the most important outcome for this diagnostic problem, the obtained result can be considered satisfactory, yet suggesting the need to further refine the diagnostic decision rule using more data. Notably, the diagnostic model in the form of a decision tree (Figure 1) provides a visually convenient form to evaluate multiple diagnostic parameters. Such a form could be used by any physician, even without access to a computer, and even by a patient himself.

Here we compare the present method with the commonly used fracture risk evaluation methods: QFracture, FRAX and Garvan fracture risk calculators. QFracture uses 26 parameters, including Type 1 or Type 2 diabetes, Parental history of hip fracture/osteoporosis, Dementia, Cancer, Parkinson's disease, Rheumatoid arthritis. FRAX uses 11 parameters, including Parent Fractured Hip, Rheumatoid arthritis, Secondary osteoporosis, Femoral neck bone mineral density (BMD g/cm^2). The Garvan fracture risk calculator uses 5 parameters, including actual BMD. These methods' sensitivity and specificity are, respectively: for QFracture – 61.4% and 90.9%, FRAX – 43.6% and 90.9%, and Garvan – 28.7% and 90.8% [3].

In terms of sensitivity and specificity, our method is significantly inferior to QFracture, but quite comparable with FRAX and Garvan. However, the QFracture calculator uses such parameters as Type 1 or Type 2 diabetes, Dementia, Cancer, Parkinson's disease, Rheumatoid arthritis, which may not yet be present at the age of 40-50 or may not yet be manifest. Also, the "Parental history of fracture/osteoporosis" may be obscure. Similar difficulties may arise for FRAX that use the parameters Parent Fractured Hip, Rheumatoid arthritis, and secondary osteoporosis. In addition, FRAX and Garvan, using the parameter bone mineral density (BMD g/cm^2), require special

dosimetry measurements. For QFracture, the literature also notes the problem of "inappropriate source data," acknowledging the need to develop new methods for hip fracture risk assessment [4].

In contrast, our method uses parameters of routine blood work. Unlike the FRAX and Garvan methods, our method's sensitivity and specificity are balanced (58.1% and 54.0%, respectively). Furthermore, the present method allows performing the practical risk evaluation after any routine blood test. Thus, it may be presumably advantageous to consider the test's overall cost-benefit analysis, utilizing such established cost-benefit criteria as cost-effectiveness (affordability), cost-consequence, and cost-utility sensitivity and cost of tests [34]. Though the precise cost-benefit analysis yet remains to be performed following further test validation. Another practical advantage of the proposed method is that it establishes an age boundary (threshold) for the risk group attribution.

Notably, the prediction of risk groups for diseases is a highly complex problem, with diagnostic rules commonly yielding rather low sensitivity values (in the range of 30-60%) [35-38]. Yet, the ability to indicate potential subjects at risk, even with relatively low certainty, using simple, inexpensive and readily available clinical biomarkers, can represent a significant advance for preventive medicine. Yet, it should be noted that the present study was conducted in a single medical center, on a limited, specific and homogenous geriatric population. Thus, this study may not be directly generalizable for the entire population due to the specific geriatric population examined. With the addition of more data from more medical centers and more data from the outpatient and general community, it may be possible to apply the present methodology to develop further clinically applicable, interoperative and accurate predictive tools.

Despite the present limitations, this model's practical application for identifying risk groups and preventing hip fractures has already been piloted at the Shmuel Harofe Geriatric Medical Center, Israel. Thus, we examined 28 subjects younger than 80 years old for the potential risk of hip fractures using the decision rule. Of the 28 examined subjects younger than 80 years old, 19 were indicated with a fracture risk below 80 years old (within their age group) and 9 with a fracture risk for subjects 80 years old and above. The former group of younger subjects is the target risk group of interest, insofar as the main purpose of the present model is to indicate the risks for the younger subjects and suggest preventive recommendations. The examined subjects were hospitalized at the Shmuel Harofe Geriatric Medical Center, due to functional decline following brain damage or prolonged hospitalization in a general hospital, yet without hip fractures. As a part of the treatment, these patients are instructed for reconditioning and a healthy lifestyle. At the admission, such patients undergo a physical examination by a multidisciplinary care team and undergo physiotherapy and occupational therapy at the rehabilitation department, emphasizing exercise to increase muscle strength, body balance, and walking to reduce the risk of falls consequent hip fractures.

Conclusion

The proposed methodology could be reliable to develop a predictive diagnosis and preventive treatment for the emergence of hip fracture in specific groups of geriatric patients. Such algorithm along with additional data, opens the opportunity to create further clinical models, and potentially computer programs, for the evaluation of the risk of hip fracture, in different age groups, based on routinely measured diagnostic parameters. The finding of an enhanced risk of a hip fracture at a younger age may pinpoint a stronger need for preventive measures, including pharmacological means, nutritional supplementation, exercise, preconditioning, assistive technologies and other lifestyle modifications. With the additional data on interventions, such algorithms can be used not only for early risk evaluation, but also for the evaluation of success of potential therapeutic interventions and for recommending specific early preventive interventions for the groups at risk.

List of abbreviations

NMI: Normalized Mutual Information

BMD: Bone mineral density
WBC: White blood cells
TH: Threshold

Ethical Issues

The study was approved by the Institutional Review Board of Shmuel Harofe Geriatric Medical Center, Israel (IRB Approval No. 53, 13 July 2017). The patient data used in this research were anonymized prior to the study.

Conflict of Interest

The authors declare that they have no conflict of interest.

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