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ORIGINAL INVESTIGATION

Predictors for a good recovery after subacute geriatric care

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Background and aims. We wanted to investigate eight different geriatric assessment tests regarding the prediction of 1) a good recovery (ability to return to own home or transfer to further rehabilitation), and 2) a poor recovery (discharge to nursing home, hospice, acute hospitals or death) in elderly patients treated in a subacute geriatric hospital ward.

Methods. Consecutive 664 community-dwelling patients aged ≥ 70 years, transferred from acute medical and geriatric wards to a subacute geriatric ward were included. Demographic data and eight different geriatric assessment tests were recorded, and odds ratio for having a good versus poor recovery was assessed with logistic regression analysis.

Results. Improvement in Barthel index (OR = 6.77, 95% CI 3.41-13.45, $p < 0.001$) and the Tinetti scale (OR 4.58, 95% CI 2.36-8.89, $p < 0.001$), along with the absence of symptoms of depression (OR = 2.19, 95% CI 1.04-4.59, $p = 0.04$) and cognitive impairment (OR = 2.19, 95%CI 1.10-4.30, $p = 0.02$), were significantly associated with a good *versus* bad recovery in logistic multivariate regression analysis. Significant collinearity ($R > 0.75$, $p < 0.001$) was demonstrated between several of the functional assessment tests.

Conclusions. Functional assessments with Barthel index at admission to the subacute ward and one day before discharge, as well as evaluation with MMSE and GDS once during the stay in the subacute ward, gave the optimal prediction of short term recovery. Further assessment with other overlapping functional tests may be redundant.

Key words: Subacute care, Older patients, Rehabilitation, Recovery, Depression

INTRODUCTION

Hospitalization in older patients is associated with functional decline and increasing dependency [1-3]. Some patients are not able to return directly to their own home and need further care to regain their functional capacity. Subacute care focuses on specialized inpatient multidisciplinary geriatric treatment and rehabilitation as a complement to acute and curative medicine [4 5]. In 2011 a 19-bed Italian subacute care ward was established as part of the geriatric department at the Fondazione Ospedale Poliambulanza in Brescia, Northern Italy, to offer multidisciplinary geriatric based treatment for patients that started medical treatment in an acute hospital ward, but have not yet recovered to the extent that is possible to discharge the patients to their own home [6]. At the same time, a complete and extensive comprehensive geriatric assessment (CGA) schedule, including eight different geriatric assessment tests, was introduced for patients admitted to all geriatric departments in Northern Italy [7]. Earlier studies on patients admitted to Italian acute and intensive geriatric wards

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have demonstrated that inability to regain function during hospitalization was associated with higher 3 month mortality [8 9]. Accordingly, the assessment schedule in the subacute ward also included assessments before the acute hospitalization and during the stay in the subacute ward, to be able to follow the trajectory of the potential functional loss in these patients.
In clinical practice it is important to evaluate the cost and benefits of geriatric assessment, given the rather low-predictive power of screening instruments [10]. After three years of extensive CGA of all patients admitted to the subacute care ward, we wanted to assess the usefulness and predictive value of the different assessment tests regarding whether the patients would experience a good versus poor short-term recovery. Special attention was paid to examine the functional trajectories during the stay in the subacute ward. To our knowledge, no such study has been performed on patients treated in a subacute geriatric ward.

METHODS

Design and setting

This study is part of a prospective, observational, cohort study that enrolled 664 homedwelling consecutive patients ≥ 70 years treated during 2011-2014 in the subacute hospital geriatric ward after acute hospitalization. The setting and the patients have been described in detail in a recent paper [11]. The optimal goal of the stay in the subacute unit was that the patients should be able to return to their own home within 40 days.

Patients and inclusion criteria's

In addition to age ≥ 70 years and being home dwelling before the acute hospitalization, the patients should have a rehabilitation potential, be circulatory and respiratory stable and not have a terminal illness. Patients with cognitive impairment were admitted if they had medical needs and the cognitive decline was not the reason for the admittance.
A majority of the patients were admitted from the departments of internal medicine, cardiology, pulmonology, and acute geriatric departments, most of them with cardiovascular diseases or infections. No patients were admitted with fractures, after elective orthopaedic surgery or after a recent stroke.
The different geriatric assessment tests were performed in > 95% of the patients, except GDS, that was performed only in patients without major cognitive impairment and MMSE ≥ 15, (n = 494 (74%), as the GDS questionnaire is regarded unsuitable for patients with major cognitive impairment.

Subdivision of patients into good and bad outcome after subacute care

The patients that were able to return home (n = 420) and patients discharged for further geriatric rehabilitation (n = 85), were defined as having a good recovery. The rest of the patients that needed readmission to an acute hospital ward (n = 41) were discharged to nursing home (n = 58), to hospice (n = 9) or died during the stay in the subacute ward (n = 47), were defined as having a poor outcome.

Geriatric assessment tests

CGA was performed with the following geriatric assessment tests, all performed by the doctor in the subacute ward.
Barthel index sub score (hereafter referred to as BI), was recorded 2 weeks before the acute hospitalization (by asking the patient or their relatives) and at admission to the subacute ward and the day before discharge, by observing the patient. BI is a questionnaire that scores 10 different ADL-items (feeding, bathing, grooming, dressing, defecation, bladder function, ability to use the toilet, transfer, mobility and climbing stairs). The range of scores is 0-100, higher scores indicates better function [12].
The Tinetti scale (Tinetti) was performed at admission and the day before discharge. This test includes assessments of physical ability, mainly of balance and moving. The range of scores is 0-28, higher scores indicates better function [13].
The Blaylock Discharge Planning Risk Assessment Screen (BRASS) includes questions of age, living situation, previous hospital admissions, number of medical problems and drugs, cognition, functional status, behaviour pattern, mobility and sensory deficit. Lower scores indicate better function and scores > 20 may indicate that the patient needs alternative level of care [14].
Scala III A (Index of Intensity of Assistance) is an Italian "ad hoc scale", divided into 12 items, each indicating progressive functional dependence in ADL and need of assistance. The range of scores is from 0-4, higher scores indicate increasing dependence [7].
The Clinical Dementia Rating (CDR) is a five item cognitive rating scale based on interview with the caretakers. The range of scores is from 0 (no dementia) to 5 (severe dementia) [15].
Mini Mental Status Examination (MMSE) is assessing the patients with different questions related to cognition. The range of scores is 0-30, higher scores indicates better function [16]. MMSE was performed at admission and the day before discharge and the best of these values were included in the present analysis.
Geriatric Depression Scale (GDS), a 15 item

questionnaire were performed at admission and the day before discharge, higher values are associated with depression [17]. In the regression analysis, GDS was stratified into two groups, GDS < 6, indicating no geriatric symptoms, and GDS ≥ 6, indicating symptoms of depression. The discharge GDS value, assumed to be the most representative of the patients` mental status, was included in the multivariate analyses.

Cumulative Illness Rating Scale (CIRS) measures 1) comorbidity and 2) disease severity. The range of scores is from 0-5, higher scores indicates higher comorbidity and disease severity, respectively [18].

Statistical analysis

Continuous data with a normal distribution were presented as mean (standard deviation) and compared with Independent-Samples T test. Continuous data with a non-normal distribution were presented as median (min-max) and compared with the Mann-Whitney U test. Categorical data were presented as numbers (percentages) and compared with Chi-Square test. The p-values were two-sided and $p \leq 0.05$ was considered to be statistically significant. Collinearity was assessed with two-sided Pearson correlation test.

For identifying the clinical characteristics that were independently associated with having a good outcome, odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using logistic regression models. The characteristics associated with $p < 0.25$ in univariate analysis were noted as likely predictors and included in multivariate, logistic regression models. In this analysis, $p \leq 0.05$ was considered to be statistically significant.

Only explanatory variables not demonstrating significant collinearity (defined as $R > 0.75$, $p < 0.001$, Table II), were included in the multivariate analysis. Accordingly, only the admission BI and Tinetti scores and not the discharge scores were included in the multivariate model demonstrated in Table III. Since there was a highly significant covariation between the BI and Tinetti assessment tests, each of these variables were tested in two different multivariate models. All the analyses were performed using the Statistical Package for Social Science (IBM SPSS 20), for Windows.

Ethics

All patients gave a written, informed consent for the treatment of personal data at hospital admission and the study was approved by hospital Ethical board. No experimental interventions were performed.

RESULTS

Differences between the trajectories of patients experiencing a good or bad outcome

Table I shows the characteristics of all the patients and patients with a good and bad recovery after acute hospitalization and subacute care. Overall, the patients in the good recovery group had clinical important better scores on nearly all of the geriatric assessment tests.

As shown in Figure 1, the loss in functional status in relation to the acute disease was substantial, with a median, equal reduced BI score of 40 in both groups. The patients in the good outcome group already before hospitalization had a higher BI score than the patients in the bad outcome group, and this difference increased further during subacute care, as more of the patients in the good outcome group experienced functional improvement and increased BI scores, as compared to the patients in the poor outcome group (Fig. 1). As a result of this, more patients with good outcome were able to return to their functional level before the hospitalization (39%), as compared to patients with bad outcome (15%). The same trend of improved functional gain in the good outcome group was seen when the functional trajectory was assessed by the Tinetti (Tab. I).

Covariation between different functional assessment tests

As represented in Table II, significant collinearity was demonstrated between several of the different assessment tests.

Predictors for patients having a good recovery

Table III demonstrates the unadjusted and adjusted OR for the association between different variables and a good outcome. While several of the functional tests were significantly associated with a good recovery in univariate analysis, only improvement in BI or Tinetti, based on assessment performed at admission to the subacute ward and the day before discharge, were associated with a good outcome, in the multivariate analysis shown in Table III. Thus, a BI or Tinetti increase of any value was associated with a 6 and 4 fold increase, respectively, of the patients having a good outcome. In addition, both a GDS score < 6, indicating no depression, and a MMSE score ≥ 24, indicating no cognitive impairment, were associated with a 2-fold increase for the patients to have a good outcome.

Table I. Differences between patients with good and bad outcomes after subacute care.

	N*	All patients	Good outcome	Poor outcome	p-value
	664	664 (100%)	505 (76%)	159 (24%)	
Demographic characteristics					
Live alone	655	212 (32%)	163 (33%)	49 (31%)	0.36
Male sex	664	293 (44%)	216 (43%)	77 (48%)	0.23
Age	664	82 (6)	82 (6)	82 (7)	0.66
Education (years)	657	5 (0-20)	5 (0-20)	5 (0-20)	0.82
Two weeks before admission					
CDR	636	0.53 (0.92)	0.43 (0.80)	0.89 (1.18)	< 0.001
BI pre	657	85 (0-100)	85 (0-100)	70 (0-100)	< 0.001
Assessment during stay in subacute care					
Blaylock scale	655	21 (5)	20 (5)	24 (6)	< 0.001
BI admission	657	40 (0-100)	40 (0-100)	20 (0-100)	< 0.001
BI discharge	648	60 (0-100)	70 (0-100)	20 (0-100)	< 0.001
Tinetti scale admission	658	6 (0-28)	7 (0-28)	1 (0-28)	< 0.001
Tinetti scale discharge	651	18 (0-29)	20 (0-29)	1 (0-28)	< 0.001
Scala III tot	650	2.9 (0.3)	2.9 (0.32)	3.0 (0.28)	0.004
CIRS severita	650	1.8 (0.3)	1.7 (0.3)	1.9 (0.3)	< 0.001
CIRS comorbidity	650	2.5 (1.4)	2.4 (1.3)	3.1 (1.5)	< 0.001
MSSE (best score)	619	25 (0-30)	26 (4-30)	21 (0-30)	<0.001
Cognitive impairment (MMSE < 24)	619	244 (40%)	170 (35%)	74 (59%)	< 0.001
GDS admission	502	4 (0-14)	4 (0-14)	4 (0-14)	0.47
GDS discharge	494	3 (0-15)	2 (0-15)	4 (0-12)	< 0.001
Depressive symptoms (GDS ≥ 6)	494	56 (11%)	38 (9%)	18 (26%)	< 0.001
Delirium at admission (cat)	659	125 (19%)	86 (17%)	39 (25%)	0.002
Change in fictional status					
BI loss at admission[a]	640	40 (0-100)	40 (0-90)	40 (0-90)	0.90
Improved BI score [b] (nom)	649	20 (0-75)	25 (0-75)	0 (0-65)	< 0.001
Improved BI (cat)	649	510 (79%)	449 (90%)	61 (41%)	< 0.001
Improved Tinetti score [b] (nom)	654	8 (0-26)	8 (0-26)	0 (0-24)	< 0.001
Improved Tinetti (cat)	654	506 (77%)	444 (89%)	62 (40%)	< 0.001
Return to pre BI [c] (cat)	640	212 (33%)	192 (39%)	20 (15%)	< 0.001

CDR, Clinical Dementia Rating scale, BI, Barthel index, I-ADL, Instrumental – Activities of Daily, Living, CIRS, Cumulative Illness Rating Scale, MMSE, Mini mental state examination, GDS, geriatric depression scale, (15 item), cat= categorical, nom= nominal

Continuous variables are characterized as mean (standard deviation), median (min-max values), categorical variables as number (%) of patients in each outcome group.

*Number of patients assessed [a]BI score 2 weeks before admission – BI score at admission, [b]Score at discharge – score at admission, [c]Return to same BI score as 2 weeks before hospitalization

Table II. Collinearity between different geriatric assessment tests.

Assessment tests	R-value
BI discharge and Tinetti discharge	0.92
BI admission and Tinetti admission	0.82
Improved* BI and Improved Tinetti	0.77
BI admission and BI discharge	0.78
BI admission and BRASS	0.72
CDR and MMSE	0.79

For description of the assessment test, see the Methods section

*Score at discharge – score at admission

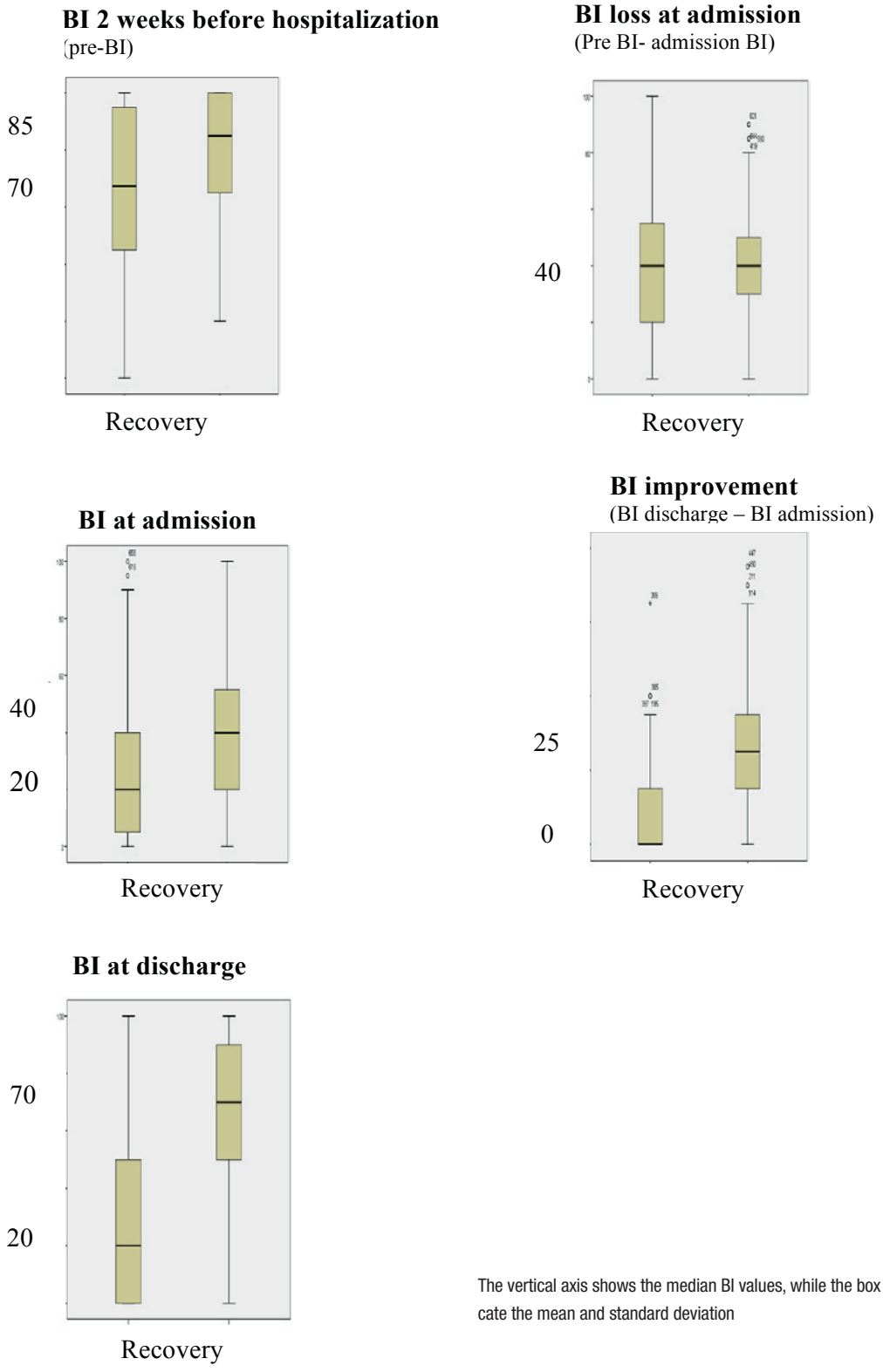

Figure 1. Trajectories of functional status before and during subacute care in patients experiencing a poor (columns to the left) and good (column to the right) recovery.

Table III. Univariate and multivariate regression analysis for predicting a good *versus* bad outcome with two separate multivariate models including either BI sum score or the Tinetti scale.

	Univariate			Multivariate					
				Model 1, Barthel Index			Model 2, Tinetti scale		
	R	95% CI	p	R	95% CI	p	R	95% CI	p
Age	0.99	0.97-1.02	0.67	-			-		
Education	1.01	0.96-1.06	0.67	-			-		
Male sex	0.91	0.83-1.70	0.36	-			-		
Live alone	1.05	0.71-1.56	0.79	-			-		
Geriatric assessment									
BI 2 weeks pre admission	1.03	1.02-1.04	< 0.001	0.99	0.97-1.01	0.17			
BI loss at admission[a §]	1.00	0.99-1.01	0.70	-			-		
BI admission	1.03	1.02-1,04	< 0.001	1.01	0.99-1.03	0.36			
BI discharge[#]	1.04	1.04-1.05	< 0.001						
Any improvement in BI*	12.15	7.82-18.88	< 0.001	**6.77**	**3.41-13.45**	**< 0.001**			
Return to pre BI[b]	3.74	2.25-6.21)	< 0.001	1.77	0.89-3.53	0.10	2.06	1.04-4.11	0.04
Tinetti admission	1.08	1.05-1.11	< 0.001				0.99	0.95-1.04	0.68
Tinetti discharge[#]	1.14	1.11-1.17	< 0.001						
Any improvement in Tinetti*	11.28	7.34-17.34	< 0.001				**4.58**	**2.36-8.89**	**< 0.001**
Blaylock scale[§]	0.88	0.85-0.92	< 0.001	0.98	0.89-1.07	0.66	1.01	0.94-1.10	0.75
Scala III tot[§]	0.35	0.16-0.73	0.005	1.42	0.51-3.92	0.50	1.53	0.57-4.08	0.40
GDS admission < 6	1.19	0.75-1.92)	0.46	-					
GDS discharge < 6	3.52	1.87-6.61)	< 0.001	**2.19**	**1.04-4.59**	**0.04**	**2.43**	**1.20-4.92**	**0.01**
MSSE ≥ 24	1.09	1.06-1.12	< 0.001	**2.19**	**1.10-4.30**	**0.02**	**1.97**	**1.05-3.71**	**0.04**
CIRS severita[§]	0.28	0.16-1.50	< 0.001	1.38	0.33-3.5.81	0.66	1.01	0.26-3.91	0.99
CIRS comorbidity[§]	0.74	0.65-0.85)	< 0.001	0.94	0.71-1.20	0.66	0.96	0.74-1.25	0.75
Delirium at admission	0.62	0.40-0.96	< 0.001	1.80	0.61-5.30	0.19	1.53	0.55-4.27	0.42

OR= odds ratio, CI= confidence interval, BI= Barthel index, CIRS= Cumulative Illness Rating Scale, MMSE= Mini mental state examination,

MMSE > 24 indicates no cognitive impairment, GDS= geriatric depression scale, 15 item, GDS < 6 indicates no depressive symptoms.

[#]not included in multivariate analysis due to collinearity with other variables

[‡]OR were estimated using logistic regression models and adjusted for the covariates as described in the Methods section

[a]BI score 2 weeks before admission – BI score at admission, [b] BI score day before discharge – BI score 2 weeks before hospitalization

[§]Variables are per unit increase, *Score at discharge – score at admission

DISCUSSION

The present study demonstrates that the ability to achieve improvement in functional status during subacute care, the absence of symptoms of depression and absence of cognitive failure were independently associated with a good versus a bad recovery after acute hospitalization and subacute geriatric care. These results are rather encouraging, since both functional loss and depression can be managed by therapy.

Other studies have demonstrated that functional status is related to a good or bad outcome, including mortality, after hospitalization [8 19 20]. The present study indicates that the patients who improved their BI or Tinetti score during the stay in the subacute ward were 7 or 5 times more likely to have a good versus bad recovery. This shows the importance of following the patients' trajectory of functional status during the hospital stay, rather than just measure one single and static measure. This has also been demonstrated in a population of intensive care geriatric patients in our hospital [9]. While the BI pre-admission may give information on the patients` past health status, the admission BI may mirror the impact of the acute disease, and the improvement or lack of improvement in BI during the hospital stay may express the individual response to a disease and its treatment. The measurement of ADL function with BI (or Tinetti) may therefore give information about illness severity beyond that provided by comorbidity and laboratory data [21 22].

The significant covariation between the four functional assessment tests, the BI, the Tinetti, the BRASS and

the Scala IIIA, imply that some of them may be redundant and therefore might possibly be substituted by other more relevant assessment tests, for example of frailty and nutritional status. The lack of predictive value of the BRASS and Scala III, in predicting recovery, may justify the removal of these tests in the fixed admission schedule. The Tinetti scale includes quite extensive testing of the patients and is rather time-consuming. At the same time, the Tinetti score was strongly correlated to the BI score, however, the predictive value was lower than that of the BI, concerning the association with a good recovery. We therefore conclude that, from a clinical point of view, assessing the functional status simply by recording BI score at admission to subacute care, and one day before discharge, gives the best trajectory of the patient's functional recovery potential. The usefulness of BI assessments and its association with recovery has been demonstrated in several other studies [8 19 22].

Patients without symptoms of depression were more likely to have a good recovery than patients with symptoms of depression. These results are in accordance with earlier studies concluding that older hospitalized patients with depressive symptoms are at higher risk of unfavorable outcome and mortality [23-25]. Significant higher values of GDS were recorded on admission (indicating that the patients were more depressed) (Tab. I) than one day before discharge. However, this is most likely due to the acute mental stress of the hospitalization and transfer to the subacute ward, and a GDS performed at this time may give false results regarding whether the patient is depressed or not. Accordingly, we conclude that GDS is an important and valuable assessment tool, however, this test should optimally be performed once, sometime after admission, but before discharge, when the patient is not under acute stress of the acute hospitalization and transfer to the subacute ward.

Patients without symptoms of cognitive impairment were two times more likely to have a good recovery than patients with symptoms of cognitive impairment. The MMSE assessment at admission and one day before discharge demonstrated a strong correlation. Performing this test at admission, when the patient may be under acute stress, may be an extra burden both on the patient and the examiner, and we recommend that also this assessment should be performed only once during the stay in the subacute ward, before discharge, when the patients are more adjusted to the hospital situation. Patients treated in the subacute ward, in general, had not yet recovered fully from their medical condition, and most of them had a substantial functional loss. Thus they were not directly comparable to patients in an acute medical/geriatric hospital unit or to patients in a geriatric rehabilitation unit, but rather share characteristics of both groups. Many of the patients in the subacute ward, and especially those with a poor outcome, share the characteristics of frail old people with reduced physical, cognitive and mental status, in addition to reduced ability to cope and recover after the acute disease [26]. The present study, indicating that both functional loss, depression and cognitive impairment were associated with recovery after subacute care, is in accordance with a literature review of Campbell et al., concluding that risk assessment in patients after acute hospitalization is complex, and that both functional status and cognitive status affects the outcome in older hospitalized medical patients [27].

A limitation of the present study is that we have only reported short term recovery, while only follow up over time can confirm the importance of improvement in ADL, depressive symptoms and cognitive impairment, as predictors of future recovery. Furthermore, the patients were recruited from the same area and treated in a single institution; thus, the generalizability of the study may be limited, and the results of the present study cannot be used to tailor subacute care to individual patients. The strength of the study is a very high inclusion rate and that extensive functional assessment tests were performed on nearly all of the patients. The adjustment for several possible confounding factors permits a more confident interpretation of the findings.

We conclude that assessing the functional status with BI at admission and during the hospital stay, before discharge, as well as performing GDS and MMSE once during the stay, may give the best prediction of recovery after subacute care. Assessment with BI gives the optimal prediction of short term recovery, and further assessment with some of the other functional tests may be redundant and could be substituted with the assessment of frailty and nutrition.

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ORIGINAL INVESTIGATION

Reliability of serum procalcitonin concentration for the diagnosis of sepsis in elderly patient with chronic kidney disease

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Background and aims. Sepsis is complicated by high mortality in hospitalized patients. Procalcitonin (PCT) is a validated tool in the diagnosis of sepsis in both adults and aged patients. Several studies demonstrated the reliability of PCT in adults with chronic kidney disease (CKD), but this has not been studied in the geriatric population. Thus, we aimed at evaluating the reliability of PCT in a group of elderly patients with CKD.
Methods. 382 subjects (mean age, 78.9 years) were consecutively enrolled and stratified in two groups at the time of the admission based on the absence or presence of CKD, defined as estimated Glomerular Filtration Rate (e-GFR) less than 60 ml/min/1.73 m^2. These two groups were further divided according to the presence (SEPSIS/NO CKD, n = 41; SEPSIS/CKD, n = 45) or absence of sepsis (NO SEPSIS/NO CKD, n = 147; NO SEPSIS/CKD, n = 149), and the serum PCT was analyzed.
Results. PCT was highly sensitive and specific in patients presenting with sepsis and no CKD. The mean serum PCT concentration in the group SEPSIS/CKD was significantly higher than in NO SEPSIS/CKD (21.00 [5.83 to 97.00] ng/ml *vs* 0.90 [0.24 to 1.32] ng/ml, $p < 0.001$). However, the PCT threshold value was 1.7 ng/ml (sensitivity 91.1%, specificity 88.6%) as compared with the currently used threshold value of 0.5 ng/ml (sensitivity 93.3%, specificity 30.2% in our population study).
Conclusions. Our study confirms the diagnostic reliability of PCT for the diagnosis of sepsis in elderly patients with CKD. Nevertheless, we suggest to apply a cut-off of 1.7 ng/ml in this population.

Key words: Circulating procalcitonin, Chronic kidney disease, Sepsis

INTRODUCTION

Sepsis is defined as a systemic inflammatory response secondary to an acute infection [1]. The incidence of sepsis and sepsis-related mortality has increased over the past 30 years, particularly in elderly people and it is now the 10th leading cause of death in the United States [2 3]. Approximately 750,000 people per year are affected by severe sepsis, and more than 50% of the affected population is over 65 years old [4]. Since the aging population is increasing worldwide, the incidence of sepsis is expected to raise in the future. In aged patients, the atypical symptoms and presentation can make sepsis difficult to diagnose clinically, leading to a delay in both diagnosis and initiation of therapy, thus resulting in increased mortality [5-8]. Assessment of procalcitonin (PCT) level in serum may be helpful in rapid diagnosis of sepsis [9]. PCT is the precursor of calcitonin produced by thyroid C cells circulating in the blood at very low concentrations (< 0.05 ng/ml) in healthy subjects; during bacterial infections, PCT production increases rapidly in all parenchyma [10 11]. PCT production is stimulated by both cytokines and bacterial endotoxin or lipopolysaccharide [12]. The utility of PCR is not only due to the

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rapid increase in the serum concentrations, but also to the rapid cleavage in case of an effective empirical treatment [6 10 11]. In patients with chronic kidney disease (CKD), PCT levels are higher than in subjects with normal renal function, and it is demonstrated that these levels are reduced after hemodialysis [13]. Thus, it is conceivable that a standard cut-off of 0.5 ng/ml could be less specific. We designed the present study to evaluate the diagnostic validity of PCT in the diagnosis of sepsis in geriatric patients presenting with CKD.

PATIENTS AND METHODS

The study was conducted at the Department of Medicina Interna Universitaria, "Ospedali Riuniti" in Foggia (Italy). We recruited 382 consecutive patients aged 65 or older. The exclusion criteria were the following: age < 65 years, active cancer, musculoskeletal trauma or recent surgery. Two groups were formed according to diagnosis of CKD (NO CKD; CKD). CKD was defined as estimated Glomerular Filtration Rate (e-GFR) less than 60 ml/min/1.73 m^2 at the time of admission.

Patients of both groups were divided according to the absence or the presence of sepsis (NO SEPSIS/NO CKD; SEPSIS/NO CKD; NO SEPSIS/CKD; SEPSIS/CKD). SEPSIS was defined as the presence of Systemic Inflammatory Response Syndrome (SIRS) plus suspect or proven infection with radiologic or blood culture. SIRS diagnosis was defined by the presence of two or more of the following criteria: white blood cells (WBC) > 12000/mm^3 or < 4000/mm^3, heart rate > 90 beats per minute, body temperature < 36°C or > 38°C, respiratory rate > 20 breaths per minute or a $PaCO_2$ < 32 mmHg [14].

Patients included in the NO SEPSIS groups who presented with febrile episodes or leukocytosis during hospitalization were excluded.

At the hospital admission time laboratory tests such as WBC count, erythrocyte sedimentation rate (ESR), serum ferritin, C-reactive protein (CRP), uric acid and creatinine were assessed. PCT was measured by electrochemiluminescence, and the standard cut-off value was established at 0.5 ng/ml, according to the most recent literature [15-17].

STATISTICAL ANALYSIS

Comparison between continuous variables was performed using Student's T-test or Mann Whitney's test and expressed as mean ± standard deviation of the mean (SD) or median (Interquartile Range, IR). Nominal and categorical variables were analyzed by the Chi-Square test and expressed as *n* (%). The impact of CKD as well as sepsis presence on the circulating levels of PCT was analyzed by two-way analysis of variance (ANOVA), using CKD as row factor and sepsis as column factor. For the diagnosis of sepsis, PCT sensitivity and specificity were calculated by receiver operating characteristic curve (ROC) analysis. Statistical tests were performed using SPSS 20 software analysis. Power analysis was performed by the GPower Software.

RESULTS

We enrolled 382 consecutive patients divided in two group based on renal function: patients without CKD (NO CKD group, n = 188) and patients with CKD (CKD group, n = 194). The patients were divided according to the sepsis diagnosis: 296 (77%) without sepsis and 86 (23%) with sepsis. Baseline characteristic are summarized in Table I. There were no significant differences among septic and no septic patients as regards age, serum ferritin, as well as creatinine and e-GFR. The percentage of women was significantly higher in the non-sepsis group ($p < 0.03$). The prevalence of co-morbidities in the enrolled patients is summarized in Table II. The percentage of patients presenting with ≥ 3 co-morbidities was not different among the CKD and NO CKD groups. The most common comorbidities in both groups were hypertension, chronic obstructive pulmonary disease (COPD) and diabetes mellitus.

The mean value of WBC and ESR, as well as the median value of CRP and PCT were significantly higher in the groups with sepsis than in no septic (Tab. I). The two-way ANOVA showed that the presence of CKD ($F = 5.072$, $p < 0.0001$) or sepsis ($F = 6.09$, $p < 0.0001$), as well as the interaction between these two variables ($F = 4.339$, $p < 0.0001$) influenced serum PCT values. Post-hoc analysis demonstrated that, while there were no significant differences in circulating PCT from CKD and NO CKD groups without sepsis, septic patients with CKD presented with higher PCT levels as compared to those with NO CKD (Fig. 1).

The sensibility and specificity in the NO CKD group using normal PCT cut-off (< 0.5) were respectively 95.1% and 87.8% (AUC 0.987) (Tab. III). Very interestingly, the sensibility and specificity using normal PCT cut-off (< 0.5) were 93.3% and 30.2% respectively in the CKD group.

We performed receiver operating characteristic curve (ROC) analysis to establish PCT value with better sensitivity and specificity for the diagnosis of sepsis in the CKD group. Results showed a cut-off value of 1.7 ng/ml with sensitivity 91.1% and specificity 88.6% with Area Under the Curve (AUC) 0.932 (Fig. 2, Tab. III). The

Table I. Baseline characteristics of elderly patients without and with chronic kidney disease (CKD). Data are presented as mean ± standard deviation, median (interquartile range) or *n* (percentage) as appropriate. Statistical differences were assessed by student's t-test for numerical variables and chi-square test for categorical variables.

	NO CKD			CKD		
Characteristics	**NO Sepsis n. 147**	**Sepsis n. 41**	***P value***	**NO Sepsis n. 149**	**Sepsis n. 45**	***P value***
Age, years	77.7 (± 7.9)	78.0 (± 8.2)	0.84	80.3 (± 7.7)	79.6 (± 8.4)	0.60
Sex, F	74 (50.3%)	13 (31.7%)	0.03	84 (56.4%)	20 (44.4%)	0.46
ESR, mm/h	48.8 (± 31.4)	77.6 (± 26.0)	< 0.001	56.7 (± 32)	69.7 (± 33)	0.02
CRP, mg/l	45 (7.00 to 97.50)	124 (66.0 to 187.9)	< 0.001	32.2 (7.5 to 109.8)	188 (82.6 to 260.8)	< 0.001
Ferritin, ng/ml	380.4 (± 42.6)	295.4 (± 56.2)	0.23	379.4 (± 81)	371 (± 47)	0.96
WBC, /ul	8655 (± 345)	14053 (± 6768)	< 0.001	10131 (± 747.9)	15521 (± 1031.1)	< 0.001
Creatinine, mg/dl	0.78 (± 0.21)	0.81 (± 0.19)	0.32	2.0 (± 1.3)	1.9 (± 0.8)	0.67
e-GFR, ml/min/1.73^2	95.99 (± 30.3)	94.98 (± 26.5)	0.85	36.69 (± 14.2)	36.21 (± 11.98)	0.84
Comorbidities ≥ 3 (n. patients)	64 (43.5%)	17 (41.5%)	0.81	103 (69.1%)	34 (75.6%)	0.41
PCT, ng/ml	0.07 (0.05 to 0.30)	8.5 (2.80 to 16.23)	< 0.001	0.90 (0.24 to 1.32)	21.00 (5.83 to 97.00)	< 0.001

Abbreviations: F: female; ESR: erythrocyte sedimentation rate; CRP: C protein reactive; WBC: white blood cell; PCT: procalcitonin.

Table II. Prevalence of co-morbidities of elderly patients without and with chronic kidney disease (CKD). Data are presented as *n* (percentage). Statistical differences were assessed by chi-square test.

	NO CKD			CKD		
Characteristics	**NO Sepsis n. 147**	**Sepsis n. 41**	***P value***	**NO Sepsis n. 149**	**Sepsis n. 45**	***P value***
Hypertension, *n*	86 (58.5%)	25 (61.0%)	0.86	104 (69.8%)	29 (64.4%)	0.58
Diabetes, *n*	45 (30.6%)	12 (29.3%)	0.98	75 (50.3%)	25 (55.6%)	0.61
Heart failure, *n*	29 (19.7%)	8 (19.5%)	0.99	54 (36.2%)	9 (20%)	0.05
Atrial fibrillation, *n*	31 (21.1%)	6 (14.6%)	0.50	51 (34.2%)	14 (31.1%)	0.86
Ictus, *n*	17 (11.6%)	4 (9.8%)	0.74	15 (10.1%)	6 (13.3%)	0.71
IHCD, *n*	24 (16.3%)	9 (22.0%)	0.49	43 (28.9%)	11 (24.4%)	0.70
Cirrhosis, *n*	11 (7.5%)	3 (7.3%)	0.97	11 (7.4%)	4 (8.9%)	0.82
COPD, *n*	46 (31.3%)	23 (56.1%)	0.001	58 (38.9%)	13 (28.9%)	0.29

Abbreviations: COPD, chronic obstructive pulmonary disease; IHCD, ischemic heart chronic disease.

analysis performed by Gpower software indicated 0.99 statistical power.

DISCUSSION

PCT is a validate marker to recognize bacterial sepsis in patients with symptoms and signs of infections [10]. PCT concentration increases in the serum within three to six hours from the development of sepsis without systemic mycoses, localized infection or SIRS. These features make the PCT a great tool for rapid differential diagnosis [13]. A systemic bacterial infection can be excluded, when the serum PCT level is < 0.5 ng/mL in SIRS patients, but it is strongly suggested if PCT > 2.0 ng/mL; a level of ≤ 2.0 ng/mL, indicates the need for re-examination after 6 to 24 hours when bacterial infection or sepsis is suspected [18].

Clinical manifestations of infection or sepsis in the elderly may be atypical compared to young adults. This can make it difficult for early diagnosis especially in the elderly with co-morbidities [8 19]. Results on the reliability of PCT to diagnose infection in aged patients are controversial. Infact, a previous study failed to demonstrate a good efficiency of PCT to detect infection in elderly people admitted to acute geriatric wards; the Authors suggested that the lack of sensitivity may be linked to the low severity of infection or to the aging process *per se*, but neither age nor comorbidity decreases the specificity of PCT [20]. Nevertheless, the ability of PCT to

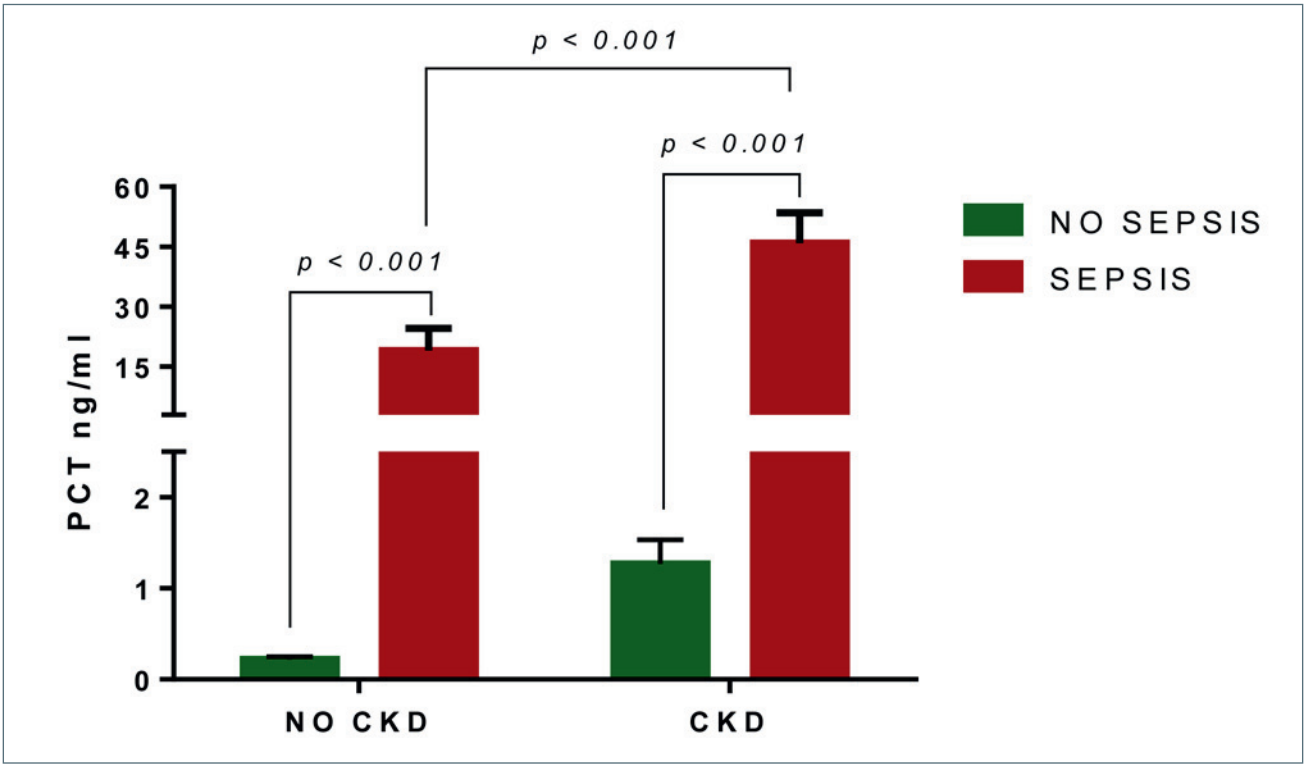

Figure 1. Serum procalcitonin (PCT) levels in all groups of studied patients. Statistical differences were assessed by two-way ANOVA and Tukey's as *post hoc* test. Abbreviations: CKD, chronic kidney disease.

Table III. Stratification of the studied population based on PCT cut off sensibility and specificity for the diagnosis of sepsis. Data are presented as *n* (percentage).

	NO CKD group		CKD group	
PCT Cut-off	**NO Sepsis n. 147**	**Sepsis n. 41**	**NO Sepsis n. 149**	**Sepsis n. 45**
< 0.5, ng/ml	87.8% (129)	4.9% (2)	30.2% (45)	6.7% (3)
≥ 0.5, ng/ml	12.2% (18)	95.1% (39)	69.8% (104)	93.3% (42)
	100% (147)	100% (41)	100% (149)	100% (45)
< 1.7, ng/ml	98.6% (145)	9.8% (4)	88.6% (132)	8.9% (4)
≥ 1.7, ng/ml	1.4% (2)	90.2% (37)	11.4% (17)	91.1% (41)
	100% (147)	100% (41)	100% (149)	100% (45)

Abbreviations: CKD, chronic kidney disease.

differentiate sepsis from localized infections or SIRS in elderly patients was demonstrated effective in another report [21].

Chronic kidney disease (CKD) is a substantial concern in the elderly, with both an increasing incidence of treated kidney failure with dialysis as well as a high prevalence of earlier stages of CKD [22]. Different results are reported for the reliability of PCT in CKD. A previous study concluded that PCT is not a reliably sensitive or specific diagnostic test for bacterial infection in patients with renal impairment when using a single threshold, although at a threshold of 0.5 ng/mL, it does have a reasonable specificity for predicting bacterial infections and a reasonable negative predictive value for predicting bacteremia [23].

Moreover, in patients with CKD a low diagnostic reliability of the current standard PCT cut-off values was shown, and a higher threshold (0.75 ng/ml) was proposed [13]. PCT levels can also increase during organ perfusion or after a severe cardiogenic shock [24,25].

To date, there have been poor data about the diagnostic reliability of the PCT in elderly patients with CKD.

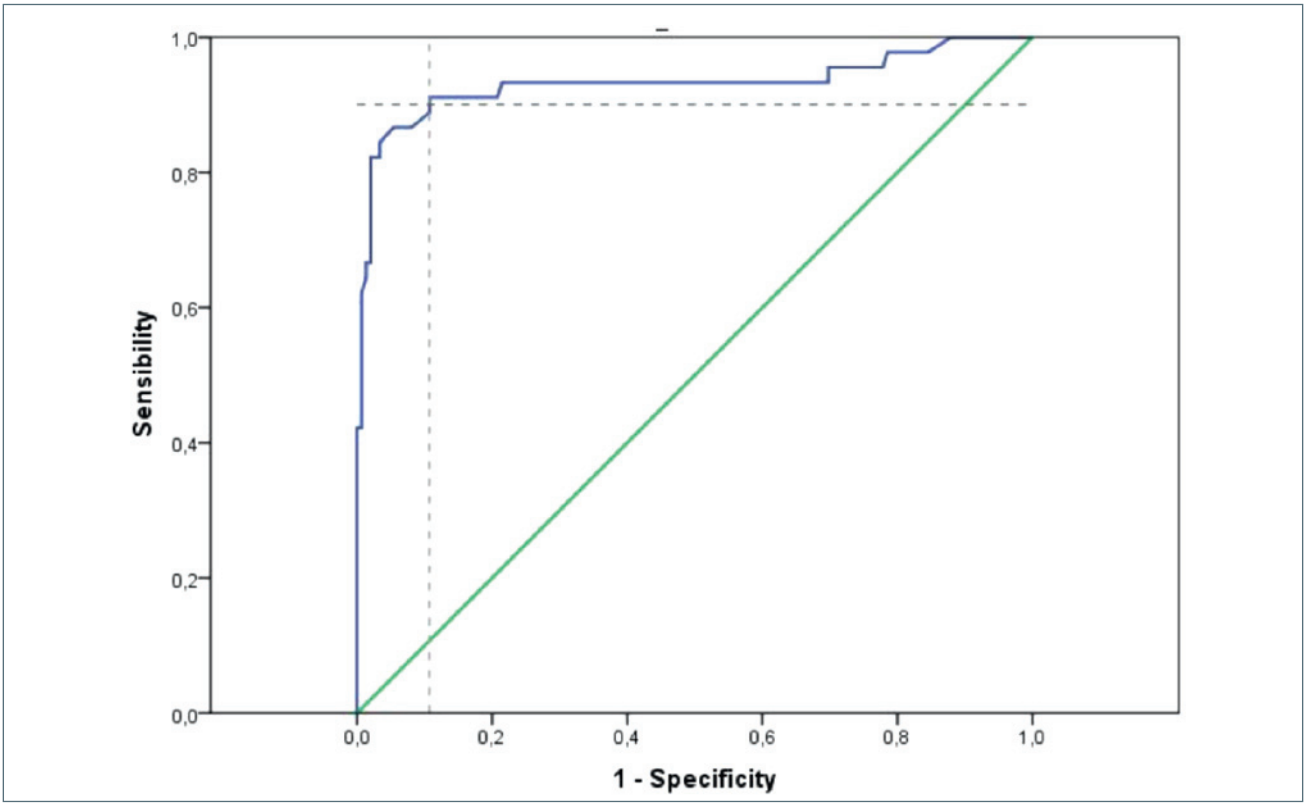

Figure 2. Area under the receiver operating characteristic curve for procalcitonin PCT cut off in the diagnosis of sepsis (AUC 0.932).

The present study confirmed the strong correlation between WBC, ESR, CRP and PCT and inflammation, showing a significant increase in geriatric patients with sepsis. However, there are differences in elderly with CKD as compared with patients with normal renal function. Our results showed that the threshold of 0.5 ng/ml in group with sepsis and renal impairment presents a high sensibility but a poor specificity for the diagnosis of sepsis. This is consistent with previous findings about the impact of renal function on serum PCT [26 27] but not in the elderly, where PCT confirms its sensibility and specificity [21]. Previous studies have shown that co-morbidities and renal impairment are associated with increased levels of cytokines, particularly IL-6, which can contribute to the inflammatory state [28-30]. This could be a possible mechanism linked to higher PCT values in elderly patients with CKD, since this pro-inflammatory cytokine is associated with increased levels of circulating PCT during sepsis [31 32]. We confirmed the significant correlation between several variables in patients with CKD with or without sepsis like WBC, PCR and PCT. We found performing the ROC curve, the value of 1.7 ng/mL as cut-off with best sensitivity and specificity, respectively, of 91.1% and 88.6%.

We are aware of the limitations of our study. First, the type of study (single-center) and small sample size restricted further subgroup analysis. A second limitation is represented by the retrospective analysis. The timing between culture and serum procalcitonin was less exact than may have been ideal due to the retrospective nature of the study. Ideally, in a prospective study, these would have been simultaneous.

In conclusion, our data confirm the diagnostic reliability of PCT in the diagnosis of sepsis in geriatric patients with CKD. However, we suggest to use a threshold value of 1.7 ng/ml, which shown the best sensitivity and specificity. Given the imperfect accuracy, we do not recommend that the PCT test be used in isolation; instead, we suggest that it be interpreted in the context of clinical findings.

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Review

Bronchial asthma in the elderly patient

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Asthma is a heterogeneous chronic inflammatory lung disease originating from a complex interaction between individual and environmental factors. As consequence of world population ageing an increase of chronic diseases prevalence, including asthma, has been documented. Late-onset asthma may have more complex pathogenic mechanisms other than Th2-mediated pattern. Diagnosis in older subjects is not straightforward as consequence of poor symptoms perception; in adults co-morbidities are associated with different asthma outcomes. A careful assessment and management of all potential concurrent disorders is essential to achieve a better disease control and an adequate response to treatment in elderly asthmatic patients.

Key words: Asthma, Elderly, Late-onset

INTRODUCTION

The ageing of the world's population is, at least in part, the reason of increased prevalence of several chronic diseases, including asthma and chronic obstructive pulmonary disease [1].

In particular, asthma in the elderly is not a rare disorder and age-related changes in the dyspnea perception and the increasing of associated co-morbidities modify frequently its clinical presentation.

Asthma is a heterogeneous chronic inflammatory lung disease originating from a complex interaction between individual and environmental factors [2-12].

Main characteristics of asthma include bronchial hyperreactivity, reversible airflow obstruction, and tissue remodeling. The most frequent symptoms in asthmatic patients are recurrent coughing, dyspnea, chest tightness, shortness of breath and sporadic wheezing, which are also common to other respiratory diseases [13-15].

Symptoms may be triggered by several factors including respiratory infections, allergens, occupational exposures, tobacco smoke, exercise and stress; respiratory viruses are a major trigger for acute asthma exacerbations [1 6-22].

Diagnosis of asthma is made by a history of variable respiratory symptoms and evidence of variable expiratory airflow limitation. Pulmonary functional tests are essential for diagnosis; additional investigations include skin prick tests, IgE serum levels, FeNO whilst imaging procedures are more relevant for differential diagnosis [23-26].

As consequence of poor symptoms perception asthma, in the elderly, may be under-diagnosed.

Asthma exhibits multiple phenotypes arising from different clinical features and biological pathways including those involved in metabolic dysregulation [27-29].

In order to obtain effective treatment, it is important to determine the specific type of asthma. Atopic asthma is commonly characterized by type 2 helper T cell (Th2) cytokine-induced eosinophilic inflammations in the airway [30-32]. Some studies showed a strong link between genetic predisposition and early-onset of asthma [32].

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Allergic asthma commonly starts in youth and may either remit or recur in adulthood [33]; it is characterized by mast cell degranulation, amplified goblet cell hyperplasia, thickening of the sub-epithelial basement membrane, and epithelial damage [34]. By contrast, non-atopic asthma which exhibit a late disease onset and is prevalent in elderly patients, usually may display high levels of serum and sputum neutrophils [35].

Most children with persistent asthma phenotype exhibit current symptoms in adulthood, whilst around half reach remission [36]. In asthmatic children who become asymptomatic in adolescence and have a recurrence of asthma in adulthood, the disease may be misclassified as "adult-onset asthma" [37 38].

Compared to childhood-onset asthma, asthma of adult onset is prevalent among nonatopic females and shows a more severe decline in lung function despite a shorter duration of disease [39 40]. Indeed, in terms of lung function, non-atopic asthma may be even more detrimental than atopic asthma [35]. The adult-onset asthma phenotype is associated with greater corticosteroid resistance when compared with youth's eosinophilic asthma [41].

In addition, elderly patients have low serum immunoglobulin E (IgE) levels due to immunosenescence; therefore, measurement of total serum IgE for clinical asthma diagnosis is less effective [35].

Age-related changes in the respiratory system may contribute to clinical features of the disease: reduced diaphragmatic force generation and systemic inflammatory changes may occur in the elderly causing an accelerate functional decline [42].

EPIDEMIOLOGY

Asthma causes a significant public health burden and can manifest itself in any age [43].

According to the World Health Organization, 4.3% of adults around the globe received a diagnosis of asthma [44].

Adult-onset asthma has become much more prevalent recently and is now an important public health concern due to its severity and lower remission rate [45]. The mortality is high in the elderly population [46]. Older asthmatic patients typically have more severe symptoms than younger ones requiring emergency treatment or hospital admission [47]. Asthma in the elderly can be misdiagnosed or under-diagnosed due to the under-reporting of symptoms, atypical presentation, or age-related factors [48 49]. For example, dyspnea, which is one of the most common symptoms in asthmatic patients, can be considered as an age-related reduction in respiratory efficiency. In addition, in older adults, a poor response to bronchodilators, the absence of an atopic history, low skin test sensitivity, and a lack of recognized diagnostic contribute to the under-diagnosis of asthma in the elderly [50-56].

Furthermore, to avoid misdiagnoses, it is important to discriminate asthma from other airway diseases with similar features. For example, it can be difficult to discriminate COPD from asthma in older patients since both diseases are characterized by airway obstruction and dyspnea; a large number of neutrophils are associated with both COPD and non-atopic asthma [57 58].

Moreover, owing to a large number of comorbidities in the elderly, it has been observed that asthmatic symptoms in these patients have been wrongly attributed to comorbid conditions such as congestive heart failure, coronary artery disease or chronic bronchitis (Fig. 1) [42 50]. Comorbidities, such as obesity and heart disease, can confound but also complicate asthma and leave it under-diagnosed or difficult to treat [59-61], also because drugs targeting these comorbidities may interfere with asthma medications and exacerbate asthma in the elderly (Fig. 2).

In a study by Piipari et al. [62] current smokers and ex-smokers had a significantly higher risk of developing asthma compared with those who have never smoked. The authors concluded that smoking highly increases the risk of asthma in adulthood.

PATHOGENESIS AND IMMUNOSENESCENCE

Increased reactive oxygen species (ROS) levels strongly correlate with the severity of asthma [63]. These higher amounts of ROS are largely responsible for the airway inflammation observed in asthma [64]. ROS and reactive nitrogen species (RNS) play an important role during airway inflammation (65). ROS/RNS initiate the inflammatory response in the lungs by activating nuclear factor-kappa B (NF-$\varkappa$B), mitogen activated protein kinase (MAPK), activator protein-1 (AP-1), and other transcription factors [65 66]. These redox-sensitive transcription factors promote the expression of numerous pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)- 1, IL-6, and IL-8, which induce the activation of inflammatory cells within the respiratory tract [67]. Interestingly, it seems that these inflammatory cells including macrophages, eosinophils, neutrophils, and monocytes are able to generate ROS themselves in order to kill the invading bacteria [68].

In elderly adults, the lower ability of neutrophils to kill invading organisms can be attributed to a decline in their ROS production. For this reason, elderly patients are more predisposed to a variety of infections and diseases.

Bacterial stimulation of the immune system is related to

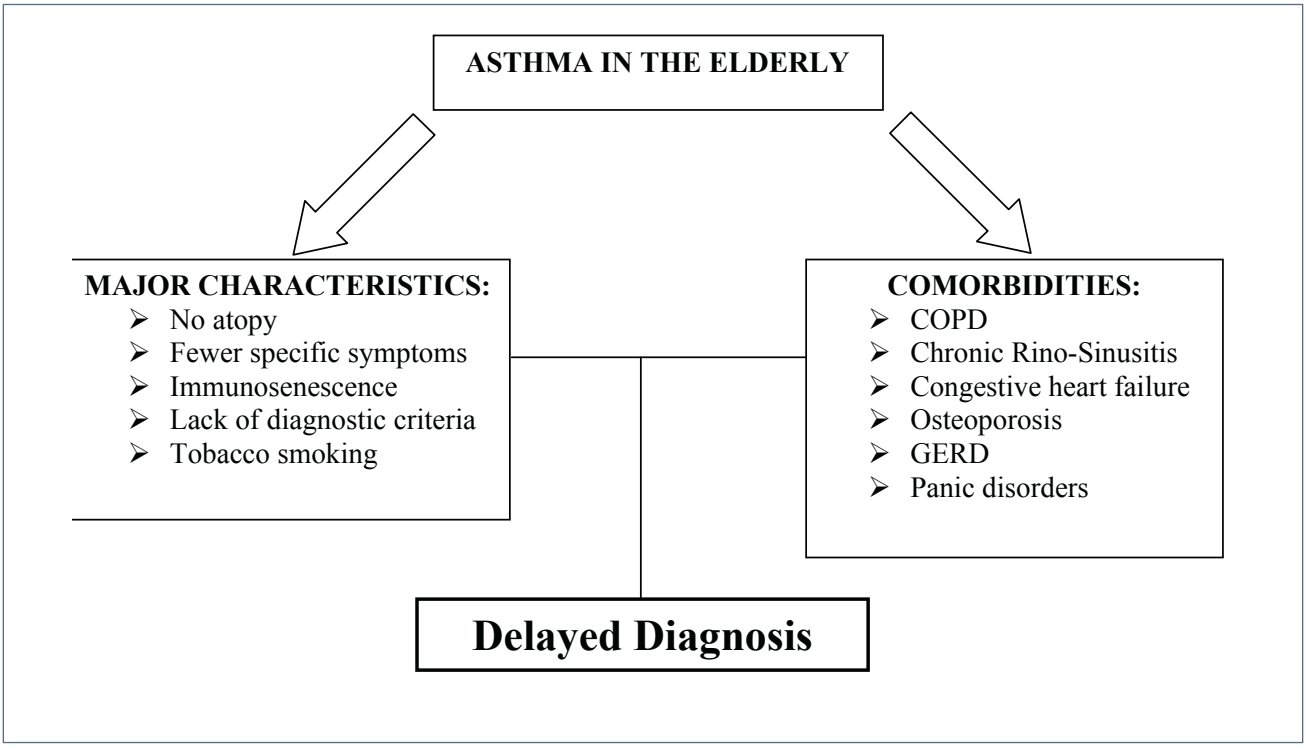

Figure 1. Asthma characteristics in elderly patients.

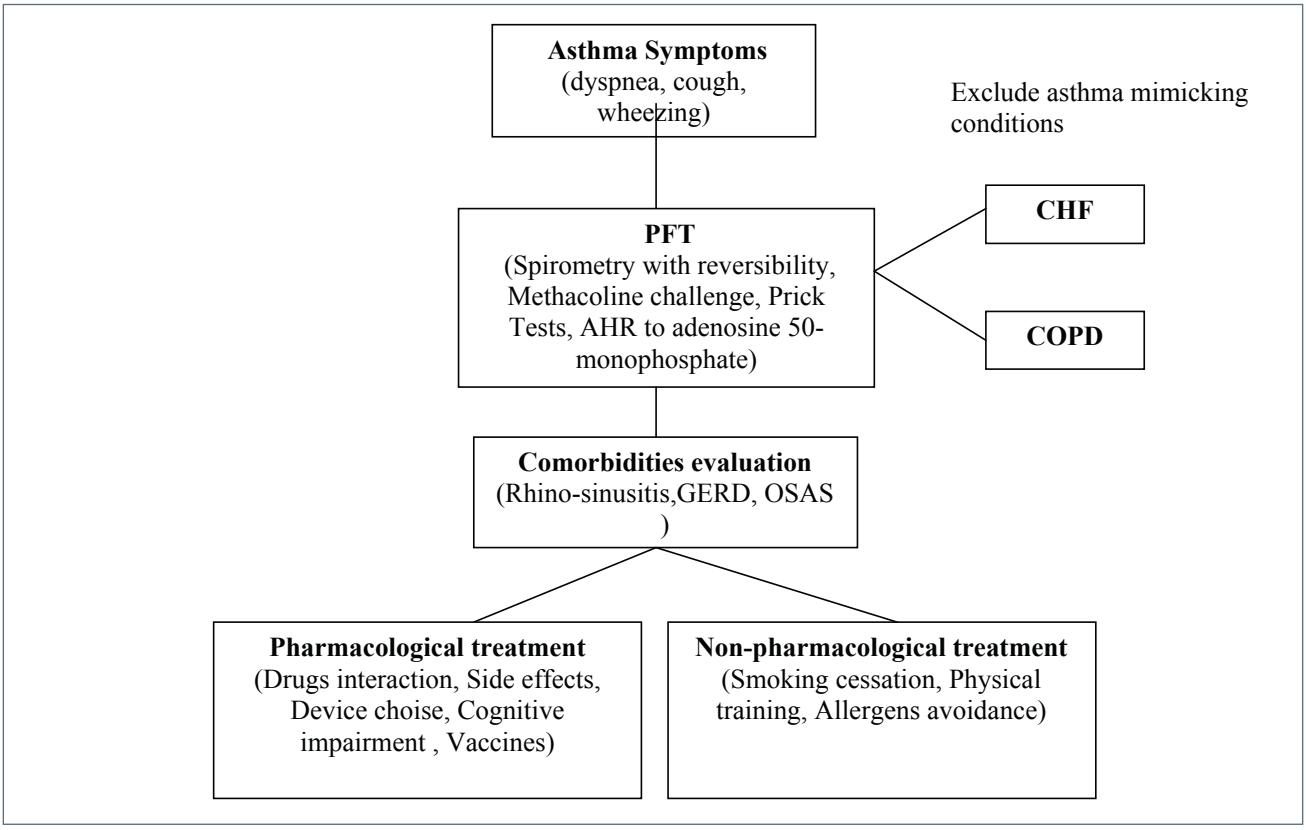

Figure 2. Diagnostic approach to asthma in older adults.

stimulation of the innate immune system and Th1 and Th17 activation in the adaptive response, it is recognized that bacterial products, such as superantigens, may be related to Th2-mediated inflammation.

Staphylococcus aureus (SA) is one of the most frequent human bacterial pathogens producing enterotoxins (SE) that act as toxins as well as superantigens.

The prevalence of SE sIgE positivity among asthmatics population varied with study populations, ranging from 14.9% to 79.1%; however, the rates showed trends to increase in older subjects and in more severe asthmatics. In non-asthmatic controls, the rate of SE sensitization also ranged widely, from 3.8% to 41.3% [69].

Older age is apparently a clinical factor to link asthma and SE sIgE. In older adult asthma, eosinophilic airway inflammation is frequently observed while no serum sIgE is detectable for common inhalant allergens. Some studies hypothesize that Th2 responses to inhaled bacterial antigens may contribute to non-atopic eosinophilic asthma in older adults. Severe asthma is another subtype which is related to SE sIgE, as suggested by two recent case-control studies [70 71].

Staphylococcus aureus commonly colonizes the human nasal mucosa, and the enterotoxins there of may provoke chronic rinosinusithis (CRS) and nasal polyp development.

FurthermoreSE-IgE sensitization is independently associated with inadequate outcomes and asthma severity in non-atopic adult patients and with severe eosinophilic asthma in the elderly [72].

Many clinical trials suggest a potential role of SA superantigens in the persistence and severity of asthma and allergic rhinitis. Bachert et al. [73] show that SE-specific IgE were more commonly found in patients with severe asthma (as assessed by measurement of FEV1, need for inhaled or oral steroid treatment, and serum level of ECP) compared to controls (62% *vs* 13%, P = 0.01).

Song et al. in their systematic review show that SE sensitization has significant associations with asthma, and in particularly, it was suggested to have relationships with the clinical reactivity and severity of asthma [69]. Immunosenescence includes age-related functional declines in the innate and adaptive immune systems [74 75]. However, the effects on adaptive immunity are more well-known than on innate immunity. Probably, altered immune responses may facilitate the pathogenesis of asthma in the elderly [76].

ASTHMA COPD OVERLAP SYNDROME (ACOS)

Obstructive ventilatory defects are a considerable challenge in elderly patients. Asthma and COPD are two major chronic obstructive airway diseases, but many patients present symptoms and features of both asthma and COPD. A graphic representation of this relationship was first presented as the non-proportional Venn diagram, reported in the 1995 American Thoracic Society (ATS) COPD guidelines [77]. In 2007 and subsequently in 2012, the Canadian and Spanish [78 79] guidelines for COPD recognized that patients with COPD and an asthma component may require a different treatment and the early introduction of inhaled corticosteroids (ICS) represents the best therapeutic option. In 2014, a GINA-GOLD committee developed a consensus based document in order to distinguishing between asthma, COPD and the overlap of asthma and COPD, so called Asthma COPD Overlap Syndrome (ACOS). In this manuscript, ACOS was described as a complex syndrome that usually involves adults (≥ 40 years), characterized by respiratory symptoms, persistent airflow obstruction with wide variations, history of doctor-diagnosed asthma, allergies and history of noxious exposures [80]. Louie et al. [81] defined ACOS as one of the two clinical phenotypes: asthma with partially reversible airflow obstruction, with or without emphysema or reduced carbon monoxide diffusing capacity (DLCO) to less than 80% predicted, and COPD with emphysema accompanied by reversible or partially reversible airflow obstruction, with or without environmental allergies or reduced DLCO. Several studies reported that ACOS becomes more prevalent in older patients [82 83]. Probably, this is due to a lifetime exposure to atmospheric pollution and environmental tobacco smoke in association to physiological changes in the lungs [7-12]. ACOS patients have more respiratory symptoms, such as dyspnea and wheezing, reduced physical activity and more frequent exacerbations compared with patients with COPD alone [84]. They also have a lower self-rated health and more impaired health-related quality of life compared with COPD. As a consequence, ACOS patients consume from 2 to 6-fold more healthcare resources than those used by asthma or COPD patients [85]. The combination of pulmonary function tests and chest HRCT showed that asthmatic elderly patients could be classificated into three different phenotypes: asthma-predominant (absence of airflow obstruction), asthma-obstructive airways disease overlap (irreversible airway obstruction without emphysema) and asthma-emphysema overlap (combination of obstructive ventilatory defect and emphysema).

Bronchial Hyper-responsiveness

Bronchial hyper-responsiveness (BHR) is often regarded as a 'hallmark' of asthma, also in the elderly. Bronchial hyper-responsiveness indicates a temporary airflow limitation when exposed to a broncho-constriction stimulus and broncho-provocation testing is frequently performed to support a diagnosis of asthma. The most

widely used is the methacholine challenge test, but histamine, exercise, eucapnic voluntary hyperventilation or inhaled mannitol tests may also be used. These tests are moderately sensitive for the diagnosis of asthma but are commonly poor specific. For example, BHR to methacoline can be found in COPD, allergic rhinitis, gastro-esophageal reflux and after viral or Mycoplasma infection

Methacholine BHR exhibits a bi-modal age distribution in the general population, increasing in the elderly, and may contribute to accelerated lung function decline and the development of asthma in later stages of life. For this reason we believe it would be helpful in elderly patients who has a mild obstruction, not reversible (FEV1 > 70%, even with history favoring the diagnosis of COPD (smoker, onset of respiratory symptoms in adulthood, radiological signs of emphysema) a methacholine challenge; the positivity to this test may involve a detachment from what is recommended by current COPD guidelines, since the presence of BHR will require treatment with inhaled steroids, in addition to a bronchodilatator (LABA o LAMA). A usefull test in diagnostic of obstructive diseases could be represented by airway hyperresponsiveness (AHR) to adenosine 50-monophosphate. Spicuzza et al. [86] showed that a single dose of inhaled fluticasone propionate (1000 mg) on AHR to inhaled AMP is able to distinguish in subjects with asthma and COPD; infact, FP caused a substantial reduction in the bronchoconstrictor response to AMP in subjects with asthma but not COPD.

IMPACT OF COMORBIDITIES IN ASTHMA ELDERLY PATIENTS

Rhinitis and rhinosinusitis

Asthma and rhinitis are considered as two different features of the same airway disease and are commonly associated to atopy.

A growing body of clinical-epidemiological investigations indicate a close relationship between asthma and allergic rhinitis. According to cross-sectional studies [87] asthma and rhinitis often coexist and share common risk factors, including atopy.

Several mechanisms might be responsible for the interaction between the upper and lower airways in asthmatic individuals; both respiratory and systemic pathways are implicated in the naso-bronchial cross-talk [88]. Loss of protective functions of the nose, aspiration of nasal secretions in lower airways (post-nasal drip), alteration of nasal nitric oxide (NO) production have been associated to lower airway dysfunctions.

Despite the small number of studies, a relationship between asthma and chronic rhino-sinusitis (CRS) has been reported in elderly patients. Song et al. observed that CRS is an independent risk factor for frequent asthma exacerbation and disease severity in elderly patients [72]. In addition, Jarvis et al. [89] showed that non-atopic CRS was positively associated with adult-onset asthma.

In patients with late-onset asthma, nasal polyposis and sinusitis have been strongly associated to severe asthma outcome. In the Severe Asthma Research Program (SARP), 54% of patients with severe asthma had a history of sinusitis *vs* 33% of those with mild asthma, and 37% of those with moderate asthma ($P < 0.001$) [90]. Also, a meta-analysis focusing the role of sinus surgery among patients with asthma has revealed that surgery had positive effects on the clinical course of asthma with comorbid chronic rhino-sinusitis [91].

These evidences indicates that disease of upper airway may influence the onset and severity of asthma and in particular appears to be associated to poor outcomes in adult-onset asthma.

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is a major upper gastrointestinal disorder seen in the elderly. In older subjects, there is a considerable decrease in the amplitude of peristaltic contraction and an increase in the frequency of non-propulsive and repetitive contractions compared to younger individuals, often referred to as presbyesophagus [92]. Salivary production slightly decreases with age and is associated with a lower salivary bicarbonate response to acid perfusion of the esophagus [93]. Finally, many drugs and diseases may adversely affect esophageal motility. In particular LES, Parkinson's disease, diabetes mellitus, cerebro-vascular, cardiovascular and pulmonary diseases are associated to esophageal dismotility. Asthma is associated with GERD in 12 to 85% of patients; the wide variation is dependent on the method used to define GERD [94]. Although an association between gastro-esophageal reflux disease (GERD) and asthma has also been reported, the underlying mechanism of this relationship remain unclear. The development of pulmonary complications in GERD is due not only to the pulmonary aspiration of refluxed material but also involves a neurally mediated reflex bronchoconstriction due to esophageal irritation by acid [95]. However, inconsistent results have been obtained in several studies on the effects of treatment of GERD on asthma outcomes. In 2003, Gibson et al. [96] showed that anti-reflux therapy did not consistently improve lung function, asthma symptoms, nocturnal asthma or the use of asthma medications. By contrast, some studies reported that PPI therapy

improves nocturnal asthma symptoms, daytime asthma symptoms, pulmonary function and decreases requirement of asthma medications in patients with GERD [97]. In elderly asthmatic patients although definitive remarks require further observations, GERD diagnosis should be considered in patients with poor symptoms control.

Sleep disturbances (SD) and OSAS

Sleep disturbances (SD), and OSAS in particular, are a common finding in patients with late asthma onset impacting on quality of life (QoL) and clinical course of the disease. OSAS is characterized by repeated episodes of upper airways occlusion that results in brief periods of breathing cessation (apnea) or a marked reduction in flow (hypopnea) during sleep. This pattern is related to oxyhemoglobin desaturation, persistent inspiratory efforts against the occluded airway, and arousal from sleep. The prevalence of OSAS increases with age, independently from other risk factors [98].

The first case reporting a possible link between asthma and OSAS was published in 1979, by Hudgel and Shruchard. Over the years more evidence were added to the knowledge about this topic. Many mechanisms may influence asthma control in patients with concomitant OSAS, including neuro-mechanical reflex bronchoconstriction, gastro-esophageal reflux, systemic inflammation.

In OSAS patients, the increased vagal tone observed occurring during apneas and could be a potential trigger for nocturnal asthma attacks in sleep apnea patients. An additional broncho-constrictive trigger is represented by hypoxia stimulation of the carotid body as results of obstructive apnea events.

OSAS patients have a higher incidence of gastroesophageal reflux. It is postulated that the increase in negative intra-thoracic pressure caused by upper airway obstruction can predispose to retrograde movement of gastric contents. GER occurring during sleep is a well-known trigger for nocturnal asthma and can provoke asthma symptoms through vagal reflexes induced by exposure of the esophagus to acid.

In individuals with OSAS, even in the absence of an inflammatory insult, chronic, low-grade systemic inflammation is characterized by increased serum concentrations of cytokines, and chemokines [99]. The origin of this systemic inflammation appears to be, at least in part, the oxidative stress induced by oxygen desaturation during sleep apneas.

OSAS has been shown to lead to many cardiovascular consequences, which may complicate a co-existing airway obstruction in asthmatic patients.

Another cause of the high incidence of OSAS in asthmatic patients may be the reduction of airway cross-sectional area and upper airway patency; the functional residual capacity of the asthmatics has been show to decline during sleep, which might partly contribute to the nocturnal increase in airway resistance [100].

A vicious cycle among GERD, obesity, cardiovascular diseases, systemic inflammation seems to contribute to worsens sleep apnea, which leads to increased severity of both asthma and OSAS.

RISK FACTORS FOR ADULT-ONSET ASTHMA

Late-onset asthma may have more complex pathogenic mechanisms other than the conventional Th2-mediated pattern which is largely mediated by atopy conditions. In adults a number of comorbid conditions are associated with different asthma outcomes (Tab. I).

Depression

Depression commonly coexists with asthma and is associated with more severe asthma and poorer asthma management. Coogan et al. reported that exists a positive association between CES-D (Center for Epidemiological Studies-Depression Scale) score and incidence of adult-onset asthma [101].

Some data suggest that depressed or sad moods elicited under laboratory conditions can produce pulmonary effects consistent with decreased airway function [102 103].

Stress is a recognized trigger of asthma exacerbation [(104)] and may cause poor adherence to asthma treatment. Conversely, remission from depression is associated with improved asthma control

The mechanism by which depression may “cause” asthma in unclear. Multiple pathways have been hypothesized: it seems that stress effects on the immune and autonomic nervous systems are relevant to the development of asthma [105], as well as co-existence of common comorbidities and inflammatory/neuroendocrine mechanisms. Major depressive disorder leads to alteration in the hypothalamic-pituitary-adrenal axis that results in endogenous glucocorticoid resistance. This, in turn, could increase vulnerability to asthma onset by biasing the immune system toward a T helper type 2 response [106 107].

Menopause

Menopause is associated with relevant hormonal and metabolic changes: estrogen levels are low after menopause, and features of the metabolic syndrome become more prevalent paired with increasing risk of chronic conditions, such as diabetes and cardiovascular diseases [108]. It has been suggested that late-onset asthma can be triggered by a change in systemic inflammation [109 110].

Sex hormone reduction has been found to be associated with a spontaneous synthesis, release, and action of

Table I. Clinical and therapeutical issues of comorbidities in elderly asthmatic patient. Impact of comorbidities on asthma outcomes.

Comorbidities		Asthma outcomes	Pathophysiology	Treatment reccomendations
Related to ageing	Depression	• Poor adherence to asthma treatment • Increase of asthma exacerbations	• Stress effects on the immune and autonomic nervous systems • Inflammatory/neuroendocrine mechanisms	Assess to avoid drug interaction or treatment failure
	Cognitive impairment	• Poor adherence to asthma treatment • Altered perception of symptoms		
	Menopause	• More frequent and severe exacerbations	• Low estrogen levels • Increase of systemic inflammation • Increasing risk of chronic conditions	
Related to shared risk factors	Rhinitis and rhinosinusitis	• Increase of asthma exacerbations • Increased severity of both asthma	• Loss of protective functions of the nose • Aspiration of nasal secretions in lower airways (post-nasal drip) • Alteration of nasal nitric oxide (NO) production	Treat independently to improve asthma outcomes
	Gastroesophageal reflux disease (GERD)	• Increase of asthma symptoms • Nocturnal asthma • Pulmonary complications	• Pulmonary aspiration of refluxed material • Neurally mediated reflex bronchoconstriction due to esophageal irritation by acid	
	Sleep disturbances (SD) and OSAS	• Increase of nocturnal asthma attacks • Increased severity of both asthma	• Neuro-mechanical reflex broncho-constriction (increased vagal tone) • Gastro-esophageal reflux • Systemic inflammation	
	COPD (Asthma copd overlap syndrome - ACOS)	• More respiratory symptoms (dyspnea and wheezing) • Reduced physical activity • More frequent exacerbations • Impaired health-related quality of life	• Persistent airflow obstruction with wide variations • History of doctor-diagnosed asthma and allergies • History of noxious exposures	
	Congestive Heart Failure and Cardiac Asthma	• Symptoms of acute and chronic cardiac and respiratory illnesses overlap • Wheezing, coughing and orthopnea	• Pulmonary edema • Pulmonary vascular congestion • Airway obstruction is probably amplified by circulating inflammatory factors and tissue growth factors	

several inflammatory cytokines [111]. Foschino-Barbaro et al. described a new phenotype of menopausal asthma, which is mainly characterized by a neutrophilic airway inflammation, non-sensitivity to steroids, poor symptom control, and higher levels of LTE-4 [112].

Airways inflammation in postmenopausal asthmatic patients seems to be different from that of patients with earlier-onset asthma, and is characterized by poorer response to anti-inflammatory treatment, as well as more frequent and severe exacerbations [110].

CONCLUSIONS

Asthma diagnosis in older subjects is not straightforward and under-diagnosis may occur as consequence of poor symptoms perception.

A multidisciplinary approach is required as co-morbidities are frequently associated to asthma in elderly patients. A careful assessment and management of all potential concurrent disorders is essential to achieve a better asthma control and an adequate response to treatment.

Performing metacholine challenge test is central to clinical disease management, also in elderly asthmatic patients; metacholine BHR seems, indeed, to be very common in old patients, with relevant implications in terms of appropriate treatment.

In this regard, significant progress in the management of asthma in the elderly could be made by introducing a tests that discriminate between asthma and COPD bronchial hyper responsiveness trough using adenosine 50-monophosphate; a single dose of inhaled

fluticasone propionate (1000 mg) on adenosine's AHR has been shown to determine a remarkable reduction in the bronchoconstriction in asthmatic subjects but not in patients with COPD [86].

Finally, the approach to asthmatic patients requires to consider the role of *S. Aureus* that seems to be largely implicated in older patients causing more severe symptoms, major airway hyperresponsiveness and worse control of the disease. For these reasons, a specific treatment against SA need to be considered to improve asthma management of in the elderly.

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IgG4 related disease in elderly: a case report

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IgG4-related systemic disease (IgG4-RSD) is an emerging autoimmune disorder that may affect several organs, with signs of organ fibrosis, storiform masses for hystopathological plasmacellular infiltration and plasmatic elevation of IgG4. This clinical condition frequently occurs in the sixth decade and may be considered an autoimmunity of the elderly; the disease may have a smouldering course with frequent misdiagnosis for the co-occurrence of comorbidity and clinical complexity.
The present case report describes the clinical case of an 81 years old woman admitted to the geriatric ward for remittent fever and functional decline. The past clinical history reported an isolated CT scan suggestive of retroperitoneal fibrosis of unknown origin with and a drug regimen that included chronic corticosteroids (prednisone 5 mg oad). The in hospital diagnostic workout demonstrated the presence of a thoracic aneurysm. Several possible diagnoses among inflammatory, autoimmune (connective tissue disease, vasculitis, sarcoidosis, amyloidosis), infectious (mycotic) or neoplastic conditions were ruled out, as well as any drug association with higher risk of retroperitoneal fibrosis.
Thus, the clinical hypothesis of an IgG4 chronic periaortitis was formulated due to the co-occurrence of all the three major components: the presence of a retroperitoneal fibrosis, IgG4 related abdominal aortitis and peryaneurysmal fibrosis. Patient's comorbidity did not allow performing the histological analysis. The present clinical case is original and adds knowledge to the 76 cases of thoracic aortitis due to IgG4 systemic disease out of the 3482 cases of disease reported so far. Further clinical investigation is needed to provide a homogeneous diagnostic workout for tailored early therapeutic intervention on the single geriatric patient. Moreover, a growing awareness of the disease is needed, especially in geriatrics, to providing a better standard of care and to improving the disease clinical knowledge and management.

Key words: Older adults, Autoimmunity, Disease

INTRODUCTION

IgG4-related systemic disease (IgG4-RSD) is a sub acute autoimmune systemic disorder, characterized by the lymphoplasmatic infiltration of different organs and tissues, leading to fibrosis. The first discovery was in 2001 [1], when the sclerosing autoimmune pancreatic disease was associated to extra pancreatic sites. The most frequently involved sites include bile ducts and gallbladder, liver, salivary glands, and kidneys, generally mimicking a neoplasia. The cardinal features are histological IgG4 expressing cells, organs fibrosis and potential elevation of serum IgG4 [2-4]. Interestingly, the mean age at diagnosis is approximately 60 years, with men prevalence (8:3); it indicates an epidemiologic trend in older adults [5]. The disease pathogenesis remains largely unclear; so far, there is increasing evidence of a Th2-driven immune response, that induces

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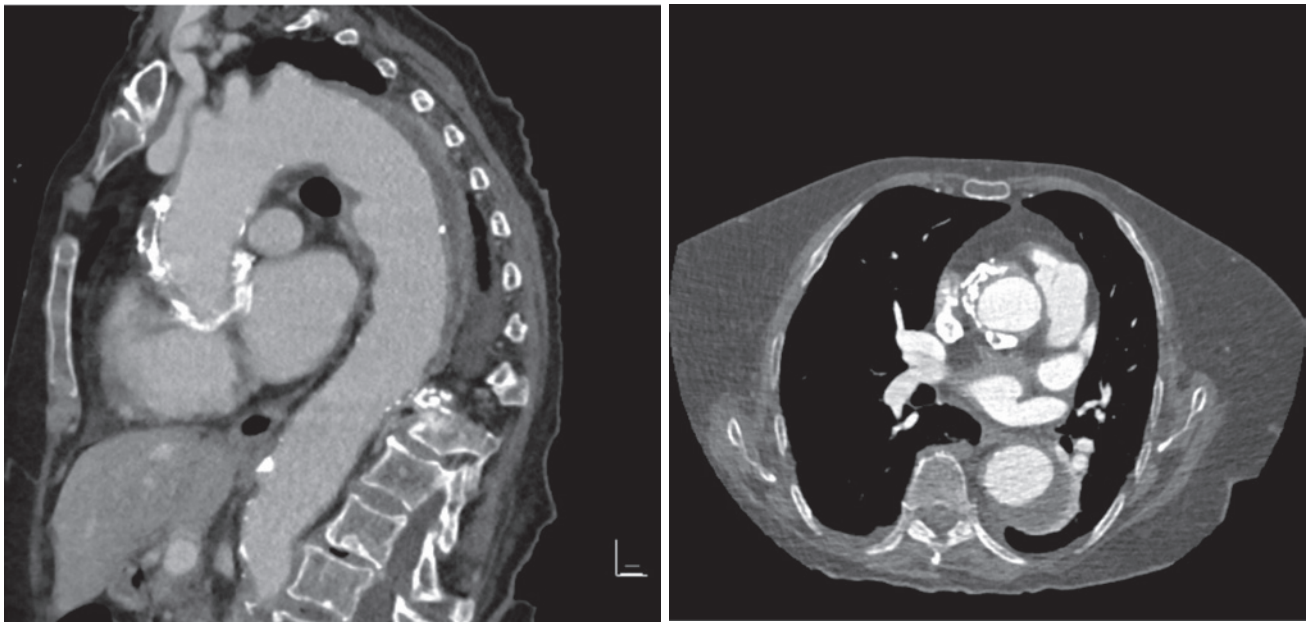
IgG4 production, associated to innate immunity activation (toll-like receptors and monocytes and basophiles) and potentially mediated by infectious agents.
The diagnosis may be challenging when unusual organs are involved or pre-existing comorbidity is present, delaying the early therapeutic interventions. The under diagnosis is particularly frequent in elderly subjects, due to the co-occurrence of multimorbidity, polypharmacy and clinical complexity.
We reported a clinical case of IgG4-related systemic disease in an oldest old woman. The clinical case is original and outlined the difficulty in the diagnostic workout of this elderly autoimmune disease due to the oldest old patient's clinical phenotype.

CASE REPORT

An old woman of 85 years was admitted to our geriatric ward (IRCCS University Hospital, San Martino Genoa, Italy) for remittent fever and functional decline. Her clinical history included arterial hypertension, osteoporosis and a polypharmacy (ramipril 5 mg oad, alendronate 70 mg oaw, calcium/Vit. D oral supplementation of 1000 mg/800 UI oad and prednisone 5 mg oad). The steroid therapy was introduced in 2009 when the patient had suffered from an abdominal colic; a previous CT scan described a storiform fibrous mass, suggestive of retroperitoneal fibrosis of unknown origin.
At the time of in hospital admission, patient's clinical examination was non informative, other than a mild low abdomen tenderness. Laboratory tests, showed a mild increase of inflammatory plasmatic markers (erythrocyte sedimentation rate, ERS 30 mm/h; C-reactive protein, CPR 10 mg/l).
The comprehensive geriatric assessment showed a functional decline (ADL 3/6, IADL 3/8), a malnutrition risk (MNA 17/30), a mild cognitive impairment (MMSE 25/30) and a moderate comorbidity status (CIRS 4/13).
The chest X-ray showed an upper mediastinum enlargement; a thorax-abdomen contrast enhanced CT and PET- CT scans showed periaortic inflammatory fibrosis, the aneurysm of the descendent aorta (max AP diameter 55 X44 mm) and of the anonym artery (max AP diameter 23 mm). A hydronephrosis, due to retroperitoneal fibrosis, that encapsulated the ureter was also observed (Fig. 1-2).
The differential diagnosis was then formulated. The patient did not show any clinical sign suggestive of either polymyalgia rheumatica or Horton's aortitis: muscles and shoulders did not show any sign of stiffness or pain. The patient did not suffer from headache, vision difficulties, jaw pain, scalp tenderness and /or temporal artery tenderness or decreased pulsation, suggestive of gigantocellular aortitis.
No medium vessel vasculitis sign was demonstrated, including myalgias, erythema or maculopapular rush.
Moreover, no small vessel vasculitis sign was observed, including polyneuropathy, migratory or transient pulmonary opacities, purpura or organs bleeding. Sarcoidosis was also ruled out due to the absence of large lymph



Figures 1-2: TC and PET-TAC scans showed periaortic inflammatory fibrosis, the aneurysm of the descendent aort (max AP diameter 55 X 44 mm) and of the anonym artery (max AP diameter 23 mm) and hydronephrosis due to retroperitoneal fibrosis.

nodes involvement, arthritis, rash or erythema nodosum and interstitial and fibrotic pulmonary disease. Systemic amyloidosis was excluded due to the absence of nephrotic syndrome, autonomic neuropathy with orthostatic hypotension. Additionally, anti-nuclear antibody, (ANA); anti-neutrophil cytoplasmic antibodies, (ANCA); extractable Nuclear Antigen Antibodies, (ENA); rheumatoid factor (RA test); angiotensin converting enzyme (ACE) resulted negative, excluding the autoimmunity hypothesis.

A serum infective panel including Syphilis test, viral, bacterial biological samples, micotic (1-3)-β-D-glucan and galactomannan blood test ruled out the infective/mycotic origin for the aneurysm. Specifically, the patients did not show any sign of bacteraemia and/or sepsis to support an adjacent aortic spreading from the infectious focus. An echocardiography ruled out the presence of infective endocarditis. No iatrogenic trauma or prosthetic arterial device was present to support a specific risk factor for mycotic aneurisms. No immunosuppression state was shown counting for opportunistic infections. The clinical hypothesis of neoplasia and or lymphoma was also clinically excluded. Any patient's drug associated with higher risk of retroperitoneal fibrosis was ruled out.

The clinical hypothesis of an IgG4 related systemic disease was formulated.

Serum levels of IgG4 were 135 mg/dl (reference values: 8-135 mg/dl) in spite of a long-term treatment with glucocorticoids [6-7], that is known to blunt the IgG4 mediated response.

The patient fulfilled most of the current diagnostic criteria for IgG4-RSD, including a clinical presentation with fibrous, storiform masses, the plasmatic detection of IgG4 [3] 135 mg/dl and the hystopathological mass plasmacellular infiltration [4].

The patient's old age did not allow the performing of histology, for an unfavourable clinical benefit to risk ratio; in keeping with that, the diagnosis of a possible IgG4 – related disease was formulated.

In particular, among the wide spectrum of IgG4 disease presentation, a IgG4-chronic periaortitis diagnosis was formulated for the presence of all the three major components: a retroperitoneal fibrosis, IgG4 related abdominal aortitis and peryaneurysmal fibrosis.

Herein, the patient had an in hospital occurrence of *Clostridium difficilis colitis*, which precluded the administration of immunosuppressants and the steroid therapy (prednisone 7.5 mg oad) was increased to provide the optimal therapeutic effect.

DISCUSSION

The present clinical case is original and adds knowledge to the 76 cases of thoracic aortitis due to IgG4 systemic disease out of the 3482 cases of disease reported so far [5 8].

IgG4-RD is not a truly new disease, as many single clinical conditions (e.g., Mikulicz disease, Kuttner tumour, Riedel thyroditis, Ormond's disease), once considered as separate clinical entity, are now included under its clinical wide spectrum [9 10].

So far, IgG4 is a multisystem disorder with a mean of 2 organ involvement; the hepato pancreaticobiliary system is the most commonly involved apparatus, followed by the parotid salivary glands anatomical system [11].

Interestingly, accumulating evidence indicates that in nearly half the cases, retroperitoneal fibrosis may be among the first clinical manifestation of IgG4-RD [9], partially overturning the rareness of the retroperitoneal fibrosis in the idiopathic form.

Male and female differed in their organ representation; male predominantly presented with periaortitis while women presented with sialodacryoadenitis [12], even if the reasons for differential organ expression in the two sexes is still unclear.

With regard to that, the present clinical case is original, referring to the IgG4 clinical presentation with chronic periaortitis in an oldest old woman.

In particular, the Ormond's disease, once recognized as isolated idiopathic disorder, is now classified within the disease grouping known as chronic periaortitis, including aortic abdominal aortitis and peryaneurismal fibrosis.

The presentation of IgG4 chronic periaortitis can be aspecific and subtle as in the reported clinical case. Common symptoms are pain in the back, lower abdomen, hydroneprhosis from ureteral involvement and storiform fibrosis of retroperitoneum, especially for long standing cases.

The diagnosis of chronic IgG4 aortitis was formulated with a level of possibility due to the lack of biopsy.

However, it is also important to note that even if the tissue biopsy is the gold standard for the diagnosis of IgG4 RS, there is increasing indication to supporting clinic pathological evidence to confirm the diagnosis. This statement is of key relevance when dealing with older and frail elderly subjects where a biopsy procedure may be of difficult performance.

Corticosteroids represent the first line treatment, but the conventional steroid sparing agents (azathioprine, mycophenolate mofetil and methotrexate) may achieve additional immunosuppression benefit, lacking prospective controlled studies to test their efficacy. The caveats to such therapeutic immunosuppressive interventions pose additional concerns when dealing with an oldest old and comorbid patient.

In this clinical case, low dose chronic steroids were initiated in 2009, inducing a clinical remission; it is known

that, low steroid dose treatment at initial treatment and low levels of serum IgG4 in cases with organ dysfunctions are associated to disease recurrence, as occurred in the clinical report [13].

The IgG4 RS represents a challenge in geriatrics, even if the disease nomenclature has been standardized, consensus have been reached and effective treatments have been identified.

In particular, the epidemiology of the disease in the older adult population is largely unknown, because of the challenges in early recognition and treatment.

The disease multi organ involvement and storiform fibrotic masses presentation often arises concern for malignancies or may be underdiagnosed in elderly, due to the co-occurrence of multimorbidity and disease smouldering courses. For instance, many elderly patients, with elevated plasmatic creatinine and urea levels, associated to gastritis, chronic thyroditis, recurrent cholangitis and chronic pancreatitis are erroneously attributed to multimorbidity and treated for the single organ clinical condition. Additionally, the presence of organ mass involvement, may be erroneously suspected of malignancy, initiating a patient's distressing and inconclusive oncological diagnostic workout.

From a pathogenetic view point, the ageing process is characterized by the immunosenescence [14], that may boosts autoimmunity; the enhanced reactivity to self-antigens and the loss of tolerance, explaining both the general inflammation (inflammaging) [15] and the rise of autoantibody (altered T- and B-cell functions, especially to the decrease in antibody affinity maturation) may constitute the pathogenetic background for it [5]. In addition, epigenetic changes associated to aging (DNA methylation, histone modifications, telomeres shortening) may also contribute to foster late onset autoimmune diseases in elderly.

IgG4-RD is a clinical issue of growing interest: to date, indeed, few studies have reported, analytically, the systemic involvement of the disease in larger cohorts of patients [10].

Anyway, greater understanding of the immunopathology of IgG4 diseases and interactions between T cell different pathways will be of key relevance in dissecting the IgG4 disease pathogenesis.

Further, greater awareness of IgG4-RD mediated pathogenesis is needed, especially in geriatrics, and a multidisciplinary collaboration is warranted to provide evidence based results and to improve the appropriateness and accuracy of the clinical management of this emerging immune mediated disease of the older age.

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Clinical, drugs interactions and pharmacogenetics evaluation of Warfarin treatment in an elderly patient: a case report

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Introduction. Cardiovascular diseases are very prevalent in the elderly population and characterized by high complexity, poor prognosis and comorbidity. Atrial fibrillation is common in elderly patients both in institutionalized in long-term care facilities and in community associated or not to congestive heart failure, but the management with anticoagulant oral therapy is highly variable and problematic.

Case presentation. Here we describe a case report on a patient treated with amiodarone and heparine for acute atrial fibrillation episodes. Three years before he underwent partial intestinal resection for bowel cancer. During Warfarin therapy a treatment with neomycin sulphate/bacitracin was started. After three days of Warfarin therapy an International Normalised Ratio (INR) value > 10 was found. No bleeding occurred, but the period of hospitalization was prolonged. After genotype assessment for CYP2C9 and VKORC1 he was found to be an intermediate metabolizer with the genotype of CYP2C9*1/*2, and homozygous for VKORC1*2/*2. By using the International Warfarin Pharmacogenetics Consortium algorithm, the estimated therapeutic Warfarin dose was 1.8 mg/day, less than a half of prescribed dose.

Conclusion. A preventive pharmacogenetic assessment could be very useful in defining the right dose of Warfarin to be administered especially in elderly patients institutionalized in long-term care facilities with comorbidity and polypharmacy.

Key words: Elderly, Pharmacogenetics, Long-term setting, Warfarin

INTRODUCTION

Cardiovascular diseases are very prevalent in the elderly population [1] and characterized by high complexity, poor prognosis, comorbidity [2-4] and more incidences of drugs side effects [5-8].

Atrial fibrillation is common in elderly patients both in institutionalized in long-term care facilities and in community associated or not to congestive heart failure [8]. A more systematic approach to decision making regarding the use of Warfarin for stroke prevention in these patients is required. Among patients receiving Warfarin, the quality of anticoagulation care warrants improvement.

Therapy in elderly is becoming more and more difficult, not only for the comorbidity that characterizes the aged patients, but also for pharmacogenomics implications that imply the raising numbers of used drugs. This brief report describes an excessive Adverse Drug Reaction to Warfarin administration at a "normal" dosage for an adult.

CASE PRESENTATION

A 76 year old man, resident in a rehabilitation care setting, was treated with amiodarone (200 mg/day

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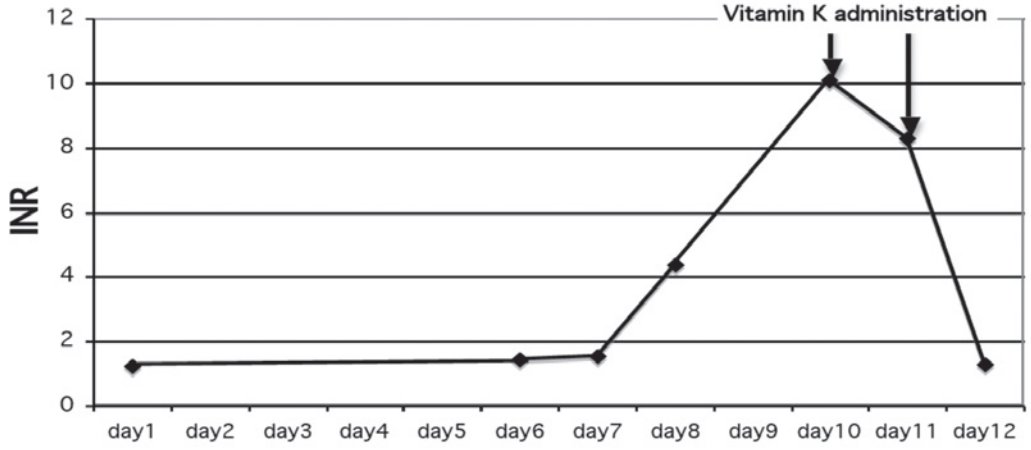
after 300 mg IV over 1 h administration) and heparin (4000 UI/day sc) for acute atrial fibrillation episodes. After three days of Warfarin therapy he showed International Normalised Ratio (INR) values > 10. Three years before he underwent partial intestinal resection for bowel cancer, and he had suffered from hypertension and dyslipidaemia. His medications at admission included acetylsalicylic acid (ASA), ramipril, lorazepam, spironolactone, pantoprazole and nitroglycerin. His diet was unchanged, and physical examination showed that vital signs were stable. During Warfarin therapy a treatment with neomycin sulphate/bacitracin was started for acute diarrhoea. After 3 days of Warfarin therapy, the INR raised to 10.1 (Fig. 1).

The treatment with Warfarin and ASA was stopped, and vitamin K administration (2.5 mg/day oral) started. Even if no bleeding occurred, hospitalization was prolonged until the patient reached full recovery. As reported by the ESC guidelines [9], the maintenance, safety, and effectiveness of INR within target range can be influenced by the pharmacogenetics, particularly of the cytochrome P4502C9 gene (CYP2C9) and the vitamin K epoxide reductase complex 1 gene (VKORC1). Therefore, the patient, after informed consent, was genotyped for CYP2C9 and VKORC1 by direct sequence and found to be an intermediate metabolizer with the genotype of CYP2C9*1/*2, and homozygous for VKORC1*2/*2 (low-dose Warfarin required). By using the International Warfarin Pharmacogenetics Consortium [IWPC] algorithm, that includes both clinical and genetic information [10], his estimated therapeutic Warfarin dose was 1.8 mg/day, less than a half of prescribed dose. After Warfarin overdosage and the pharmacogenetic determination, the patients was treated with low dose of Warfarin, and for the subsequent 5 weeks INR values fell within the 60% of optimal stable dose.

DISCUSSION

Defining the right dose of Warfarin to be administered in elderly patients with comorbidity and polypharmacy is not easy for clinical and pharmacogenetics reasons [11]. Multiple studies have clearly demonstrated an increased frequency of CYP2C9 allelic variants, such as CYP2C9*2, in patients stabilized on low dose Warfarin therapy with increased probability of extremely elevated INRs and major bleeding events as compared to the general population. At the same time, the presence of VKORC1*2 polymorphism is associated with reduced VKORC1 expression, that requires lower Warfarin doses.

Whereas stratification of thromboembolic risk is the first step in the management of patients with atrial fibrillation, several studies have shown that adherence to the guidelines is not ideal, with consequent serious implications for



INR	1.25	---	---	---	---	1.46	1.53	4.4	---	10.1*	8.3*	1.3
Warfarin dose (mg)					5	5	6.25					
ASA	x	x	x	x	x	x	x					x
Lorazepam	x	x	x	x	x	x	x	x	x	x	x	x
Pantoprazole	x	x	x	x	x	x	x	x	x	x	x	x
Nitroglycerin	x	x	x	x	x	x	x	x	x	x	x	x
Amiodarone			x	x	x	x	x	x	x	x	x	x
Neomycin/Bacitracin						x	x	x	x	x		

Figure 1. Timetable of INR values, Warfarin dosage and other drugs administration. *INR: International Normalised Ratio; (*) Vitamin K administration; (x) Drug administration.*

prognosis [12 13]. In fact, although the interactions between several drugs and Warfarin are well known, in the clinical practice many drugs with the potential for drug-drug interactions are prescribed despite the warnings. For instance, amiodarone may increase the pharmacologic effects of Warfarin by inhibiting its CYP2C9 hepatic metabolism, resulting in significant hypoprothrombinemia and bleeding, with increased anticoagulant effects becoming apparent within one to several weeks, and, in poor CYP2C9 metabolizers, a higher risk of bleeding and a faster onset of the interaction [14]. Neomycin sulphate/bacitracin are also reported to interact with Warfarin. In fact, since the drug destroys the enteric flora that synthesizes vitamin K, it is possible to observe enhanced anticoagulant activity. In this case the interaction was also complicated by a concomitant reduction of enteric surface in consequence to the previous colectomy, with changes in the absorption of nutrients. In addition, whilst a lower target INR range (1.8-2.5) has been proposed for elderly patients, probably because it is not based on large clinical trials, physicians generally do not adapt the doses of anticoagulants for old patients.

CONCLUSION

In conclusion, a global clinical evaluation and a preventive pharmacogenetic assessment with the use of a pharmacogenetic dosing algorithm (such as the IWPC) could be very useful in defining the right dose of Warfarin to be administered and, therefore, reducing the risk of an excessive increase of INR with possible bleeding complications, especially in elderly patients with comorbidity and polypharmacy.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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Time to change approach

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Key words: Dementia, MCI, Scale

Epidemiology of dementia is an extremely serious issue. The prevalence estimate in western world is increasing steadily and the figure of about 7 millions of cases [1] is turning out to be in Europe 8 millions in 2020 and over 11 millions in 2040 [2]. Moreover, dementia is one of the main contributors (5th) to Years Lived with Disability among people over 65 years aged, according to the WHO report and the economical burden in Europe increased steeply by 20% from 2010 and 2015 (from 214 to 268 billions of euro) and the forecast is not better [3].
These dramatic data, associated with population aging, will lead to an unavoidable change in the health policy-makers to face this epidemic-like occurrence. However, together with these data it is not possible to neglect the stage of the disease called mild cognitive impairment: MCI was developed in 1.7-22.6% of the study populations [4 5]. The wide range of prevalence is determined by the still controversial diagnosis and by the population studied.
At any rate, a significant part of MCI develops into dementia (annualized conversion rate ranges from 7.5 to 16.5%), thus representing an early stage of the disease [5 6].
Interestingly, some functional capacity deficits can also be observed before the onset of cognitive impairment, and the people with functional impairment and MCI is more prone to evolve in dementia in comparison to those without deficit of activity of daily living [7 8].
It should be very relevant to have a tool to evaluate the functional pattern in MCI persons. Few scales are developed for mild dementia but their utilization is complex and the scales are not specific for MCI [9 10]. The possibility to identify earlier the persons at risk could focus our clinical, diagnostic and therapeutic efforts to a smaller and more precise group of population, saving resources and improving our approach to the disease.
A recent paper of Luttenberger proposed a simple and specific method to study the functional status in MCI. The paper published on BMC Geriatrics [11] proposes, after a validation, the ETAM (Erlangen test of activity of daily living) scale. The scale in the final version consisted in 6 items of five areas specifically developed to MCI or mild dementia. The study validation was performed on a group of aged people (mean age 82 ± 8 years), most women (65-70%) with normal cognition, MCI, mild dementia or moderate dementia.
MMSE and MOCA were the tools utilized for the screening the cognitive capacity.
The Authors after a deep statistical analysis and a review of the "research version" of the ETAM scale offer the final version that they suggest can be used in all "industrialized countries" adjusting some items to the local traffic signs and currency.
The test consists in five areas selected from a wider number of topics, excluded after the statistical analysis because too easy, too difficult or repetitive: the first one is the *communication* focused on the use of a phone (6 points), the *mobility* that contains the understanding the road traffic situations (light, signs) (6 points), the *self care* implicating the drugs schedule (6 points), the *domestic life* consisting in making a cup of tea with kettle (3 points), and reading and setting time in a alarm clock (3 points) and, finally, the *economic life* with the comparison of different offers and calculations with money (6 points).

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The maximum score was 30 points: the results of the four groups identified by the MMSE and MOCA mean scores were reasonable: normal (22.3 points), MCI (17.8), mild dementia (12.7) and moderate dementia (7.2).

The scale is very interesting for several reasons. BADL and IADL show the aging sign and this new scale is updated and flexible enough; it is long time that the researchers try to find a more ecological scale for functional status, able to intercept the change of society: the ETAM scale matches with the these special needs. Moreover, the ETAM scale covers the domains of the International Classification of Functioning, Disability and Health (WHO, 2001) that includes the context and the environment in which the subject lives, it is open to future development and to different cultures (i.e. mobile phone instead to the classic phone; preparation of coffee or other beverage, and not tea; setting some digital instrument in place of alarm clock etc.). Finally, the time requested is acceptable 20-35 min and the material easily retrievable.

It is difficult to state that this test is the best available in literature, however it is a good attempt to improve the instruments that we use at this moment. I'm convinced that now it is the time to change something and to make an effort to find an approach proportional to the new information available.

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