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Keywords: Diabetes, Cardiovascular Complications, Risk prediction, biomarkers

Corresponding Author: Dr. Martin Hülsmann,

Corresponding Author's Institution:

First Author: Michael Resl, M.D.

Order of Authors: Michael Resl, M.D.; Stephanie Neuhold; Michaela Riedl; Heidemarie Abrahamian; Guido Strunk; Rudolf Prager; Martin Clodi; Martin Hülsmann; Anton Luger; Richard Pacher

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Abstract:
Background: NT-proBNP is an excellent predictor of adverse events in patients with diabetes mellitus. Due to an aging population it is of interest to determine whether NT-proBNP can predict cardiac events with equal precision in subgroups with different ages.
Design: We recruited 1395 outpatients with diabetes mellitus for this prospective observational study.
Methods: NT-proBNP, renal function, lipid status and other demographic variables were measured at baseline. The cohort was divided into three groups: Group I (609 patients under 60 years of age), group II (634 patients ranging from 60-75) and group III (152 patients older than 75). Patients were followed during a mean observation period of 11 months, 75 patients reached the defined endpoint, which was unplanned hospitalization due to a cardiac event.
Results: Mean age was 60 ± 30 years, mean HbA1c was 7.6% and mean NT-proBNP was 242 ± 437 pg/ml. In a multiple Cox regression model age (HR 11.18, $p<0.01$) and the absence of a cardiac disease (HR 0.49, $p<0.01$) were important variables for short-term prognosis. The addition of the logarithm of NT-proBNP provided independent prognostic information (HR 1.81 $p<0.01$) and significantly increased the explained variance of the model ($Chi2 = 22.93$; $df=1$; $p<0.01$). More importantly, the predictive power of this model was similar in different age-groups.
Conclusion: The prognostic information of NT-proBNP was not influenced by age and this biomarker remained a reliable predictor of short-term cardiac events in patients with diabetes mellitus aged 75 years or older.

Keywords: Diabetes, Cardiovascular Complications, Risk prediction, biomarkers

Suggested Reviewers:

***Response to review**

Dear Editor,

We want to thank you for giving us the opportunity to change our paper according to the questions raised by the reviewers. Please find our answers below.

Answers to the editor:

- Please also check that your Reference list includes relevant papers that have been published in our journal. The Editors require that at least one paper (but preferably more) from EJCPR is cited.

We have now added two relevant references.

20. Jeppesen J, Hansen TW, Olsen MH, Rasmussen S, Ibsen H, Torp-Pedersen C, Hildebrandt PR, Madsbad S: C-reactive protein, insulin resistance and risk of cardiovascular disease: a population-based study. *Eur J Cardiovasc Prev Rehabil,* 2008 15:594-598

7. Fourth Joint Task Force of the European Society of Cardiology: European guidelines on cardiovascular disease prevention in clinical practice: executive summary. *Eur J Cardiovasc Prev Rehabil,2007, 14(Supp2):E1-E40*

Answers to the reviewers:

- please limit the HR and 95CI limits to two decimals.

We have changed the Hazard ratios and 95 CI limits to two decimals.

- please limit the p value to two decimals, and used p < 0.01

The p values have also been adapted.

- the table on sensitivity etc is not very helpful. In prediction research, the emphasis would be on several variable to predict the absolute risk of an event. So, emphasis on only one measurements is not desirable. Also, the authors have indicated that the risk of an event can be predicted best with the combination of age, history of previous disease and the marker of interest. Please provide a table like that which relates the ranking of of people using the three variables and the absolute risk estimate in these groups.

We have now changed table 3 showing cumulative survival rates according to age groups and NT-proBNP values.

NT-proBNP and cardiac events in older diabetic patients

Michael Resl[1], Stephanie Neuhold[2], Michaela Riedl[1], Heidemarie Abrahamian[3], Guido Strunk[5], Rudolf Prager[3], Martin Clodi[4], Martin Huelsmann[2], Anton Luger[1] Richard Pacher[2]

[1]Department of Endocrinology

Medical University of Vienna, Austria

[2]Department of Cardiology,

Medical University of Vienna, Austria

[3]Third Department of Medicine,

Hietzing Hospital Vienna, Austria

[4]First Department of Medicine,

Kaiser-Franz-Joseph Hospital Vienna, Austria

[5]Research Institute for Health Care Management and Economics

University of Economics and Business Vienna, Austria

Running Title: NT-proBNP cardiac risk assessment in the elderly

No conflict of interest

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Address for correspondence:

Martin Hülsmann

[2]Department of Cardiology , Medical University of Vienna

Waehringer Guertel 18-20, 1090 Vienna, Austria

Phone: +43-1-40400/4374, Fax: +43-1-40400/7790

Email: martin.huelsmann@meduniwien.ac.at

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Results: Mean age was 60 ± 30 years, mean HbA_{1c} was 7.6% and mean NT-proBNP was 242 ± 437 pg/ml. In a multiple Cox regression model age (HR 11.18, $p<0.01$) and the absence of a cardiac disease (HR 0.49, $p<0.01$) were important variables for short-term prognosis. The addition of the logarithm of NT-proBNP provided independent prognostic information (HR 1.81 $p<0.01$) and significantly increased the explained variance of the model (Chi^2 =22.93; df=1; $p<0.01$). More importantly, the predictive power of this model was similar in different age-groups.

Conclusion: The prognostic information of NT-proBNP was not influenced by age and this biomarker remained a reliable predictor of short-term cardiac events in patients with diabetes mellitus aged 75 years or older.

Keywords: Diabetes, Cardiovascular Complications, Risk prediction, biomarkers

Introduction:

Patients with diabetes mellitus are at an increased risk of developing cardiovascular disease [1-3]. This cardiovascular risk is comparable to that of non-diabetics with a prior myocardial infarction [4]. Dyslipidemia and hyperglycemia contribute to a large extent to the accelerated vascular injury and atherosclerosis [5]. Insulin sensitivity and beta cell function correlate well with endothelial markers at least in patients with heart failure [6].

Several clinical risk markers such as $HbA_{1c,}$, urinary albumin to creatinie ratio, LDL-cholesterol, age, history of cardiac disease, systolic blood pressure and NT-proBNP are well established [1;7; 8; 9]. Among these markers NT-proBNP is the most promising for short-term prediction of cardiovascular events [10; 11].

Concerning age and concomitant diseases, patients suffering from diabetes mellitus represent a very heterogeneous group. Since the population in industrialized countries is aging and the prevalence of diabetes mellitus is steadily increasing, it is very important to determine if our currently used diagnostic algorithms and biomarkers are also useful in the subpopulation of older diabetic patients [12]. NT-proBNP is considered to be age-dependent for the diagnosis of congestive heart failure, therefore different cut-offs have been proposed. Regarding risk-stratification the situation is unclear [13]. Recently Frankenstein and colleagues have shown that NT-proBNP is an age-independent predictor of all cause mortality in chronic heart failure patients [14].

In the current study we tested the ability of NT-proBNP to predict cardiac events in differently aged subgroups with a special focus on older diabetic patient.

Methods:

Design

This prospective observational study included patients attending the diabetic outpatient clinic of Vienna's General Hospital and of the Hospital Hietzing Vienna between December 2005 and August 2008.

Detailed information about the design of this ongoing project has been published previously [10].

The study was conducted in accordance with the Helsinki II declaration and was approved by the ethics committee of our institution. All participants gave a written informed consent.

Medical examination

A certified nurse took a compiled medical history for each patient, with a special focus on cardiovascular disease, in order to obtain information about concomitant diseases and current treatment. Blood pressure was taken, an electrocardiogram was recorded and blood was drawn from an antecubital vein in all patients.

Analytical methods

Plasma glucose, lipid values, and serum-creatinine were measured using routine tests in a certified laboratory. Long-term glucose metabolism was evaluated by HbA_{1c}. NT-proBNP was determined using a commercially available kit (Roche Diagnostics). Kidney function (estimated glomerular filtration rate) was calculated by the MDRD formula.

Endpoint

The primary endpoint was defined as hospitalization due to a cardiac event (ischemic heart disease, chronic heart failure or heart rhythm disturbance). Data concerning mortality were obtained from the Austrian Central Office of Civil Registration (Zentrales Melderegister). Information about hospitalizations for cardiovascular disease was obtained from hospital files by a cardiologist, who was unaware of the results at index time.

Statistical Analysis:

We presented continuous variables as means ± standard deviation; categorical variables were shown as frequencies and percentages.

According to the UNO definition of age we divided our collective into three subgroups. Group I (609 patients younger than 60 years old), group II (634 patients ranging from 60-75) and group III (152 patients older than 75) [15]. Comparisons between the three age groups were calculated using an one-factorial ANOVA for continuous variables, and a chi^2 test for categorical data.

The predictive value of NT-proBNP was assessed by comparing two Cox proportional hazard models. Proportional hazards assumption was assessed and satisfied for all variables based on partial residual plots and on time interaction tests. For all continuous variables squared values and the logarithm were calculated. Only for NT-proBNP and age the logarithm outperformed the untreated data within a single variable Cox regression models. Therefore the logarithms of NT-proBNP and age were used. Variables as follows were included in both models: (1) logarithm of age (years), (2) gender (1/0), (3) duration of diabetes (years), (4) LDL-cholesterol (mg/dl), (5) GFR (mg/min), (6) absence of any cardiac disease (0/1), (6) hypertension (0/1), (7) history of smoking (0/1), and (8) insulin therapy (0/1). The first model (baseline model) was only based on the named variable, the second model used the

logarithm of NT-proBNP as an additional predictor (extended model). Differences between these nested models were assessed based on the likelihood ratio test.

Because the logarithm of age was included in the models the hazard ratio of NT-proBNP in the second model can be interpreted independently from any age effect. However, possible interaction effects between age and NT-proBNP were not captured by this model. For this reason, additional interaction terms based on dummies for the three age groups and the logarithm of NT-proBNP were created and tested as additional variables for the second model. All results from the Cox regression model were presented using hazard ratios EXP (B) per standard deviation increase.

ROC-curves were built for risk prediction in the entire cohort and in the subgroup of patients older than 75 years. To present different cut-offs for cardiac risk stratification in diabetic patients older than 75 years of age, we calculated sensitivity, specificity, negative and positive predictive value. NT-proBNP values 125 pg/ml, 200 pg/ml, 300pg/ml and 450 pg/ml were chosen as cut-offs.

The cumulative survival rate for different age-groups, the history of any cardiac event and high vs. low Nt-proBNP-levels was assessed by a Kaplan-Meier analysis.

A $p<0.05$ was considered significant in all analysis. SPSS 16.0 software (SPSS, Chicago, IL) was used for all statistical analysis.

Results:

The total study population consisted of 1395 (799 male, 596 female) patients with diabetes mellitus representing a typical unscreened collective treated at a diabetic outpatient clinic, with a mean age of 60 ± 13 years of age and a mean duration of diabetes of 13.5 ± 12.1 years. History of hypertension was present in 927 (66.5%) patients, mean systolic blood pressure was 144 ± 23 mmHg and mean diastolic blood pressure was 82 ± 12 mmHg. At baseline ischemic heart disease was present in 253 patients (18%), 40 patients (2,9%) presented with arterial fibrillation and 18 (1%) with valvular disease. Mean

HbA_{1c} levels were 7.6%. A total of 58.8 % of patients were treated with insulin, 54.8% with oral antidiabetics and 19.6% were receiving both. More demographic data in relation to the age groups are shown in Table 1.

During a mean observation period of 11 months 75 patients (4.8%) reached the primary endpoint, which was hospitalization due to a cardiac event. In group 1 13 (2.1%) patients in group 2 40 (6.3%) patients and in group 3 22 (14.5%) patients experienced a cardiac event, this difference was significant ($p< 0.001$). Overall 34 patients experienced an ischemic event (5 patients < 60 years, 20 patients between 61 and 75 years, 9 patients older than 75 years) , 24 patients (1.7%) had a rhythm event (4 patients < 60 years, 14 patients between 61 and 75 years, 6 patients older than 75 years) and 17 patients (1.2%) were hospitalized due to worsening or new onset of chronic heart failure (4 patients < 60 years, 9 patients between 61 and 75 years, 4 patients older than 75 years).

Cox regression models

First we calculated a baseline model including selected variables, which are most often suggested to be predictive for cardiac risk. Variables were entered as follows: logarithm of age, gender, duration of diabetes, LDL-cholesterol, estimated glomerular filtration rate, absence of any cardiac disease, hypertension, history of smoking and insulin therapy. In this model the logarithm of age and the absence of a history of a cardiac disease were significant predictors of the endpoint (HR 39.94, $p< 0,01$ age, HR 0.29, $p<0.01$ absence of any cardiac disease).

In a second model we added the logarithm of NT-proBNP to the baseline model (extended model). Beside the variables logarithm of age (HR 11.18, $p<0.01$) and absence of a cardiac disease (HR 0.49, $p<0.01$) the logarithm of NT-proBNP added superior independent information (HR 1.81 $p<0.01$) (Table 2).

Calculation of the -2 Log Likelihood of both models (894.54 for the baseline model and 871.61 for the extend model) proved that the extended model comprised more information (Chi^2 =22.93; df=1 ; $p<0.01$).

To prove the hypothesis that there is a significant difference of the model dependent on age-groups, terms of interactions were built and added to the model. None of those terms of interactions reached a significant level (p=n.s.), which proved a similar behavior for NT-proBNP in each group.

ROC – Curves

The ROC curves underscored the prognostic value of NT-proBNP in every age-group with an AUC of 0.87 ($p < 0.01$, CI 0.77-0.98) for patients younger than 60 years old, an AUC of 0.70 ($p< 0.01$, CI 0.60-0.79) for patients between 61 and 75 years of age and an AUC 0.73 ($p<0.01$ CI 0-68 – 0.83) for patients older than 75 years of age (Figure 1).

Table 3 shows cumulative survival rates for 24 month, based on Kaplan-Meier estimates. One can clearly identify the pattern: survival rate decreases with age, the history of any cardiac event and a high Nt-proBNP-level.

Discussion:

Natriuretic peptides like BNP and its precursor NT-proBNP are well established markers for risk stratification in patients with an underlying cardiac disease and in unselected cohorts. Recently published data confirm the prognostic value of NT-proBNP also in diabetic patients [10; 16]. The data presented here demonstrate for the first time, that although NT-proBNP concentrations increase with

age, age does not influence the prognostic power of these biomarkers. The age -dependent increase of NT-proBNP clearly reflects the tremendous increase of cardiac risk in an elderly population.

Prognostic implication

NT-proBNP is considered to be age-dependent for the diagnosis of heart failure, but for risk - stratification the situation is quite different. Frankenstein et al. demonstrated in a recent analysis of a collective of heart failure patients, that increased levels of NT-proBNP in elderly patients do not reflect age , but solely increased risk. Our data extend this information to a non heart failure risk population.

It is well established that age is a major risk factor for experiencing a cardiovascular event. A myriad of other biomarkers like serum-creatinine, CRP, HbA_{1c}, systolic blood pressure, cytokines and hormones, among them NT-proBNP, serve as surrogate markers for the endothelial and cardiovascular status of the patients. [17-20] They are all elevated in elderly patients. Our data show that increased levels of NT-proBNP and age per se are independent predictors of cardiovascular risk. NT-proBNP adds important information to a model that includes selected traditional risk factors. Of even more relevance, the increased explained variance between the different models does not differ between distinct age groups. This implies that increased levels of NT-proBNP in the elderly diabetic patient are not due to increasing age, but actually unmask increased cardiovascular risk.. Therefore our data prove, that using distinct cut-offs the negative predictive value of NT-proBNP is comparable in all age-groups analyzed. Accordingly, age and NT-proBNP concentrations could serve to identify diabetic patients with the highest risk of developing a cardiac event. Interestingly, neither duration of diabetes nor the quality of therapy (proven by HbA_{1c}) had an independent influence on short-term

cardiac events. Of the two markers age and NT-proBNP, NT-proBNP appeared to be the more powerful predictor.

An NT-proBNP concentration below 125 pg/ml is associated with a low risk of experiencing a cardiac event in the following year, also in patients aged 75 years or older.) In our cohort only one patient older than 75 years with an NT-proBNP level below 125 pg/ml died. (data not shown)

Clinical implications

The fact that in our cohort 31.8% of patients that were older than 75 years and that had an hospitalization due to a cardiac event in their medical history died prematurely underscores the importance of anticipation and avoidance of cardiac events. This has also been shown by Olsen and colleagues [13].

Studies in large cohorts of unselected patients have shown that for patients with a long duration of diabetes an intensified antihyperglycemic therapy seems to have no beneficial effects on cardiovascular outcome [21; 22]. In contrast, the STENO trial has proven that intensive therapy is able to reduce the incidence of cardiovascular events in pre-specified high risk populations such as patients presenting with microalbuminuria [23] . The same working group found that NT-proBNP adds additional prognostic information to microalbuminuria [16]. This is in accordance to our unpublished data which, proved a clear superiority of NT-proBNP to proteinuria regarding risk-stratification [11].

Consequently, it seems possible that the effects of an intensified therapy could be optimized if risk groups would be pre-specified by NT-proBNP concentrations. This would be especially relevant for elderly patients who are most at risk.

If it would be possible to modify NT-proBNP concentrations with specific therapy and if a change in concentrations would reflect an altered risk, especially in the elderly, is completely unknown and therefore open to speculation. Even in the heart failure community, which has a long tradition of NT-proBNP use the discussion on both these questions , if repeated measurements reflect therapeutic

success [24; 25] and if therapy should be guided by such markers [26], is ongoing. A retrospective analysis of the STENO study found [16], that a decrease in NT-proBNP carries prognostic information, which makes the question worth pursuing.

An issue of clinical relevance is the use of the right cut-point. As this is a rather political than a statistical question we have offered several values for a direct comparison. For risk stratification in the primary care setting safety is paramount, therefore a high sensitivity or negative predictive value are important. Concerning patient selection for intensified therapy or management a high grade of efficacy and therefore a high specificity or positive predictive value is important. Thus different cut-points can be used dependening on the specific question.

What we found striking was the low event rate in the younger population of only 2.1%. Since adverse events were independent of the duration of diabetes, this cannot be explained by the argument that younger patients have a shorter history of disease. It is unclear whether younger patients can be regarded as low risk patients per se or if additional risk markers have to be used. But, we should keep in mind, that even in younger patients the additional information of NT-proBNP is similar to the information provided in elderly patients and that at least 19% in this population are at increased risk.

In summary, The prognostic information of NT-proBNP was not influenced by age and this biomarker remained a reliable predictor of short-term cardiac events in patients with diabetes mellitus aged 75 years or older. Elderly patients with low NT-proBNP levels have a low risk of dying or experiencing a cardiac event.

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Table 1

Table 1: Demographic data

	< 60 years	61-75 years	>76 years
Duration of Diabetes (years)	11 ± 11	15 ± 12	17 ± 12
Creatinine (mg/dl)	0.95 ± 0.21	1.08 ± 0.31	1.28 ± 0.61
LDL-Cholesterol (mg/dl)	112 ± 33	103 ± 29	103 ± 33
Triglycerides (mg/dl)	187 ± 351	158 ± 111	149 ±85
HbA1c (mg/dl)	7.6 ± 1.5	7.6 ± 3.8	7.5 ± 1.1
Systolic Blood pressure (mmHg)	137 ± 21	148 ± 23	149 ± 24
Diastolic Blood pressure (mmHg)	83 ± 13	82 ± 12	79 ± 13
Weight (kg)	85.3 ± 19.8	84.7 ± 16.5	78.5 ± 16.7
eGFR (ml/min/1,73 m^2)	83.18 ± 16.79	68.80 ± 17.05	55.42 ± 15.07
NT-proBNP (pg/ml)	130 ± 250	278 ± 473	543 ± 657
No. of Patients NT-proBNP > 125 pg/ml	116 (19%)	279 (55%)	115 (76%)
No. of Patients NT-proBNP < 125 pg/ml	493 (81%)	355 (40%)	37 (24%)

Table 2

Table 2: Cox Regression Analysis

Baseline Model after the addition of the logarithm of NT-proBNP:

	Baseline Model			Model including the logarithm of NT-proBNP		
Variable	**Wald- coefficient**	**Hazard Ratio**	**Significance**	**Wald- coefficient**	**Hazard Ratio**	**Significance**
Gender	0.8926	1.2693	0.3448	0.2616	1.1358	0.6090
Duration of Diabetes	0.1689	0.9952	0.6811	0.0366	0.9978	0.8482
LDL-Cholesterol	0.0321	0.9993	0.8578	0.1263	0.9987	0.7223
eGFR	0.5464	0.9946	0.4598	0.0861	1.0020	0.7692
Presence of any cardiac disease	22.6551	0.2948	<0.001	6.6919	.04893	0.0097
Hypertension	0.6745	0.8079	0.4115	0.7917	0.7933	0.3736
Smoking	0.2716	1.2096	0.6023	0.4037	1.2657	0.5252
Insulin Therapy	0.3084	1.1536	0.5787	0.0964	1.0836	0.7562
Ln (Age)	16.2250	39.9433	<0.001	7.1713	11.1847	0.0074
Ln (NT-proBNP)				23.2544	1.8123	<0.001

Table 3:
Cumulative survival for 24 month, based on Kaplan-Meier estimates

	Age					
	< 60 years		61-75 years		>75 years	
History of any cardiac disease	no	yes	no	yes	no	yes
NT-proBNP value						
<450 pg/ml	0,98	0,96	0,96	0,85	0,91	0,84
>450 pg/ml	0,77	0,76	0,84	0,64	0,61	0,53

Figure
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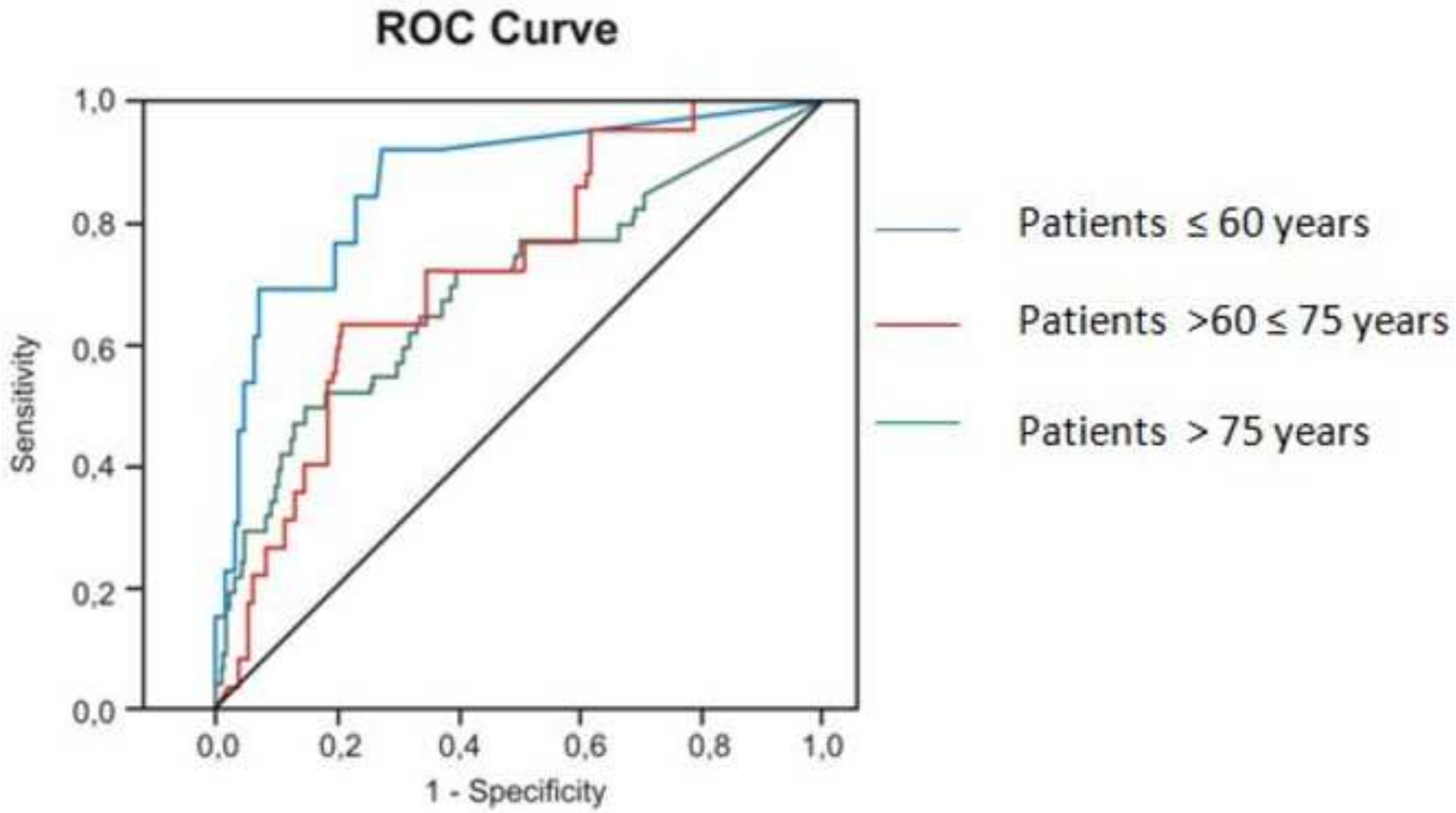

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Michael Resl M.D.
Medical University of Vienna
Department of Endocrinology and Metabolism
Waehringer Guertel 18-20
1090 Vienna

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Dear Editor,

All authors meet the criteria for authorship staded in the Uniform Requirements for manuscripts submitted to biomedical Journals.
M. Clodi designed and performed research, evaluated the data and wrote the manuscript. M. Resl performed research, evaluated data and wrote the manuscript. M. Hülsmann designed and performed research, and revised the manuscript. M Riedl revised the manuscript and participated in the collection of data. M. Elhenicky, S. Neuhold and H. Abrahamian performed research and discussed the results. R. Prager and A.Luger designed research and discussed the results. R. Pacher designed research, evaluated the data and discussed the results
All authors had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis.
All authors read and accepted the final version of the manuscript.
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Corresponding Author:
Martin Hülsmann
Department. of Medicine II,
Medical University of Vienna Währinger Gürtel 18-20,
1090 Vienna, Austria

Phone: +43-1-40400/4374, Fax: +43-1-40400/7790
Email: martin.huelsmann@meduniwien.ac.at