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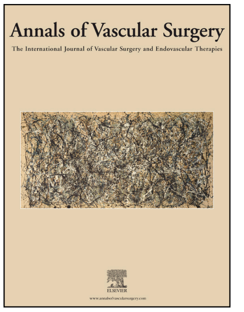

Prognostic value of aortoiliac calcification score in Kidney transplantation recipients.

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TITLE PAGE

Title: Prognostic value of aortoiliac calcification score in Kidney transplantation recipients.

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Abstract:

Background:
Kidney recipients are increasingly older with arterial disease and extended arterial calcifications. In a kidney transplantation population, the prognosis value of aortic and iliac calcifications remains poorly explored. We aimed to assess the impact of pre-transplantation Aortoiliac vascular calcifications on patients, grafts survival and cardiovascular events.
Methods:
This retrospective study included kidney transplantation patients from 2006 to 2012 for whom we had available pre-surgery abdominal computed tomography results (n=100). We designed a score to quantify Aortoiliac calcifications. Primary endpoints were patient and graft survival. Secondary endpoints were renal function and cardiovascular morbidity. Predictive performances of calcification score were assessed using area under Receiver-Operating Characteristic Curves. Patients were classified in quartiles depending on Global Calcium Score value.
Results:
The cumulated rate of death and graft loss was 13% with no significant differences for survival between quartiles. No significant difference was observed in renal function (p=0.4). Seventeen cardiovascular events were registered with a significant correlation between calcium score elevation and need of cardiovascular surgery during the follow-up (p=0.01). Global calcium score had a predictive value of 74.5% (95%CI 0.62, 0.87) with 71% sensitivity and 73% specificity.
Conclusion:
Aortoiliac calcifications do not decrease patient and graft survival. High calcium score predict cardiovascular events and procedures during the follow-up.

Main Text:

INTRODUCTION:

The population of kidney transplantation recipients has significantly changed over the past three decades. In 2012, the leading causes of kidney transplantation were diabetes, hypertension and glomerulonephritis. Changes also occurred in recipient's ages. Population of kidney recipients is older than before with half of new patients older than 60.

Along with age, prevalence of arterial disease and especially extensive arterial calcifications is increasing. This has become the leading cause of mortality among population of renal transplant recipients [1,2]. Consequences of vascular calcification have been investigated in coronary arteries [3–6]. Although the prognosis value of aortic and iliac calcifications have been well investigated in dialysis patients, it remains poorly explored in kidney transplantation population [7–9]. Recently, Imanishi et al [10] concluded that aortic calcification index can progress after transplantation, in correlation with age and post-transplant renal function, and can represent a post transplant cardiovascular event risk factor.

In this study, we aimed to assess the impact of pre-transplantation aorto-iliac vascular calcifications on patients and grafts survival to see if arterial calcifications are linked to poorer outcomes in kidney transplant recipients as well as an increased cardiovascular risk.

METHODS:

Patients

This retrospective study included kidney transplantation patients from 2006 to 2012 for whom we had available pre-surgery non-enhanced abdominal computed tomography results (n=100). During this period, 373 patients were treated. Among them, 100 underwent a non-enhanced abdominal CT prior to transplantation, which was used to calculate aortoiliac calcification score. Other 273 patients were excluded. All patients included in the study were analyzed and separated in four quartiles depending on the Global Calcium score value. Each quartile included 25 patients. CT scans were ordered as a part of the pre-transplantation screening and must have been performed within one year before transplantation. Our cardiovascular screening included basically electrocardiogram, chest x-ray. For candidates with diabetes, history of personal or family cardiovascular disease, we recommended to perform a maximum stress test or to realize from the outset an ultrasound of dobutamine stress or a scintigraphy of stress, even coronarography if necessary. We also made a complete vascular screening with echo duplex for peripheral arterial disease. All of the above patients had a complete cardiovascular pre-transplantation screening.

Calcification score

We designed a score to quantify aortic and iliac calcifications, adapted from Agatston's methodology, which initially was designed to study coronary arteries [11–13]: were considered as a calcification each surface of more than one mm^2 in which attenuation value was more than 130 Hounsfield Unit (HU) on Ultrafast CT acquisition. Patient's study was made using Siemens Somaton Definition® [14]. The investigation included renal arteries to common femoral arteries. Dose reduction by angular modulation was made using Caredose® software. Acquisition protocol consisted of 120kv beam with 0.8 pitch and one rotation every half second. Reconstruction of imaging slices was made in one mm every two mm thickness using B30 filter for soft tissues and a variation for attenuation value of 350 HU with a center at 50HU. The workstation Siemens Syngo CT 2010A® (Siemens AG 2010) was used for analysis with Ca-scoring application. Calcifications were defined as four picture elements with an attenuation value > 130HU. The operator performed automatic calculation after a selection of the region of interest. The data obtained included: the number of lesions, volume in mm3, mass in mgCaHa and Agatston equivalent, which was defined as calcium score. Scoring has been done by two different operators, independent, and blinded for clinical data to evaluate external variability. The analysis took in account calcification from aorta below renal arteries to common iliac arteries and external iliac arteries were grafts were implanted most of the time. We did not analyzed internal iliac arteries. Every calcification was analyzed, localized or circumferential, when lesion's density was above 130 HU. For all patients, a global score was first obtained encompassing infra renal aorta, common and external iliac arteries. A second score was developed, aimed at focusing on the arterial area where graft was implanted. This second score took into account the only infra renal aorta in case of orthotopic procedure or both infra renal aorta and ipsilateral iliac axes in the other cases.

Endpoints

Mean duration of follow-up was 4.18 years (±1.64). No patient was lost to follow-up. Events were defined as patient death and graft loss. The two primary endpoints were patient and graft survival. Survival rates were calculated for the global population and for each subgroup defined by quartiles of calcification score. The first secondary endpoint was the renal function evaluated one year after kidney transplantation and at the end of follow-up. We defined renal function degradation as a Glomerular Filtration Rate (GFR) decrease of more than 10 ml/min/1.73m^2 between first year post transplantation and last follow-up. The other secondary endpoint was cardiovascular morbidity. Cardiovascular events were analyzed with coronaropathy and peripheral arterial disease before and after kidney transplantation, with fatal events (myocardial infarction) and non-fatal (myocardial infarction, coronary artery bypass, percutaneous transluminal coronary angioplasty, carotid endarterectomy). Pre-transplant cardiovascular morbidity concerned all non-fatal events occurred before kidney transplantation. Total cardiovascular disease summarized coronaropathy and peripheral arterial disease in the cohort and in each quartile. Immunological variables, which could be considered as confounding factors for graft survival, were collected.

Statistical analysis:

The reproducibility of the calcium score was established from Kendall tau rank correlation method. Data were summarized in table and expressed as means with standard deviation for continuous and percentage for categorical variables. For each characteristic a one-way ANOVA was performed for quantitative variable and a Fisher's exact test for categorical data to compare quartile groups. Survival analysis was performed using Kaplan Meier method for each calcification quartile and compared by Log rank test. The predictive performances of calcification score were assessed using area under Receiver-Operating Characteristic (ROC) Curves with a confidence interval of 95%. Inter variability was evaluated using Kendall's tau (τ) coefficient. All statistical analysis was performed using R software (V 2.15.2). R core team (2012). R: A language and environment for statistical computing, Vienna, Austria, ISBN 3-900051-07-0, http://www.R-project.org/

RESULTS:

Patient's demographics:

Demographic characteristics are represented in Table 1. About surgical variables, four percent were third transplantation, 18% second and 78% first transplantation. Five percent were related to living donors. Five percent were done preemptively. Concerning demographic data, patients in the fourth quartile were significantly older than in the first quartile ($p<0,001$). Mean dialysis duration was significantly higher in the fourth quartile ($p=0,046$). No significant differences were found between each quartile for chronic kidney disease ($p=0.11$). Panel reactive antibody (PRA) average percentage for kidney recipients at the time of transplantation was 25.41%±38.3. This was not significant ($p=0.33$). To identify influence of recipient ages we also tested matching by ages. We found an average difference of 0.47 years ±10.7, which was not significant ($p=0.3$). For cardiovascular risk factors, we found the same significant difference ($p<0,01$) between each quartile for past tobacco use, cardiovascular history and post-transplantation dyslipidemia. For cardiovascular diseases, we found a significant difference in the past medical history between the four quartiles ($p=0,03$). Calcium score did not affect risk of diabetes ($p=0.2$).

Calcium score:

Mean global score was 8380 mgCaHa for the entire cohort, ranging from 0 to 25000, which was the highest value given by the software. Mean calcium score for Quartile one is 184, 2050 for quartile two, 8219 for quartile three and 23068 for the last one. This last quartile is less discriminant because 16 of the 25 patients had the same score of 25000. Concerning the two operators, Kendall's tau coefficient was 0,89 for the global score and 0,81 for the selective one. We concluded with a positive correlation the two scores since values tend to reach $\tau=1$.

Primary endpoints:

No event occurred in early postoperative period. During follow-up four deaths occurred (4%) three neoplasias and one road accident. Nine graft losses occurred (9%). One in the first quartile was due to glomerulonephritis recurrence, 2 in the 2nd quartile were due to acute rejection and hemolytic uremic syndrome. Three in the 3rd quartile due to cardiac insufficiency, post graft-biopsy infarction, and BK Virus nephropathy. Three in the last quartile were due to one cardiac insufficiency and two humoral rejections. Cumulated rate of death and graft loss was 13%. There were no significant differences in survival between quartiles. Patient and graft survival were analyzed for global and selective scores. Kaplan-Meier survival curves are displayed in figure one.

Secondary endpoints:

Nephrological data:

Mean duration of dialysis in the entire cohort was 5.93 years with a median of 2.60 years. There was a significant link between dialysis duration and global calcification score with $p=0.046$ with an increase coefficient of 32.7 per year of dialysis.

Glomerular filtration rate (GFR) was calculated by Modification of Diet in Renal Disease (MDRD) formulae using standardized Creatinaemia and expressed in ml/min/1.73m^2. Renal function was evaluated one year after transplantation and at the last follow-up (table 2).

Creatinaemia was significantly higher at the last follow-up in the fourth quartile ($p=0.046$) but this result was not significant when GFR was calculated with MDRD ($p=0.1$). 23 patients presented renal function degradation, but no significant differences were observed between quartiles for mean GFR at last follow-up ($p=0.57$). To avoid bias due to difference of follow-up we studied GFR slope of decay for each group and no significant difference was observed (p=0.4).

Cardiovascular morbidity:

17 events were registered (Table 3). There is a significant correlation between a calcium score elevation and the need for cardiovascular surgery during the follow-up (p=0.01). The area under the receiver-operating characteristic (ROC) curves was used to evaluate the prognostic value of calcium score in relation to post-transplantation cardiovascular events. The global score (Fig 2A) had the strongest predictive value: 74.5% (95%CI 0.62, 0.87) with 71% sensitivity and 73% specificity. For selective score, result was 67.6% (95%CI 0.52, 0.83) with 50% sensitivity and 81% specificity (Fig 2B).

DISCUSSION:

This study shows that even severe aortoiliac calcifications does not impaired patients and graft survival in kidney transplant recipients. Failing kidney transplants and return in dialysis are not increased in this cohort. Nevertheless aortoiliac calcium score can be considered as a risk factor for cardiovascular morbidity since high scores are predictive for more cardiac and peripheral vascular procedures. Our results are in line with results published by Imanishi et al. [10] and confirm that high calcification score is associated with higher cardiovascular morbidity.

Two aspects limit our results. First, we are presenting only 100 patients. This must be confirmed with further studies including more patients. Secondly, our mean follow-up is only 4.18 years and outcomes of secondary cardiovascular surgeries would have been better evaluated with a longer follow-up. Because non-enhanced CT was not previously systematic in pretransplant screening, we had to shorten our cohort.

Calcifications diagnosis and quantification:

Pre-transplant screening for calcification and cardiovascular morbidity must be systematic. Calcifications are important for both per-operative and postoperative period. For per-operative period, calcification increase risk of dissection, embolism, and thrombosis. Major calcifications can change standard procedure of iliac anastomosis. Some performs prior arterial reconstruction before transplantation [15,16]. This can be relevant for aneurysms or occlusive disease because of hemodynamics consequences but is not consistent with isolated calcification [17–19]. Calcified atherosclerotic plaques are less vulnerable with fewer embolisms than soft atherosclerotic plaques and less hemodynamics effects. When external iliac vessels are highly calcified preventing from cross clamping, endovascular clamping can be perform using Fogarty catheter threw femoral access. In other situation, if CT-scan shows non-calcified area, anastomosis can be performed on common iliac vessels, below-renal aorta, orthotopic position or visceral arteries. 20% of our cohort has been transplanted above iliac extern vessels.

Aortofemoral bypass or contra indication for kidney transplantation are nowadays uncommon, despite massive aortoiliac calcification [20]. For post-operative period, calcifications seem to be a risk marker for further cardiovascular procedures. Better cardiovascular outcomes have been shown if patients are included in a carefully post transplant cardiovascular follow-up. [21]. In our study, during the four years of follow-up, 18% of the patients underwent cardiac or vascular procedures. We did not find in the literature any study about cardiovascular surgery after kidney transplantation in elderly and calcified patients. Therefore we cannot say whether those 18 secondary cardiovascular procedures are normal or higher than the mean.

Renal function does not seem to be affected by severe aortoiliac calcification. In our cohort, there is no significant difference between the first and the fourth quartile for the GFR's slope of decay. The mean decrease of GFR in this study is one to two ml/min/1.73m^2/year during the follow-up, as well as the mean decrease of our entire register.

One of the main problems is quantification. Plain X-ray has been used to build a prognostic score for aortic calcification in dialysis patients. It has been found that iliac and femoral calcifications were linked to higher mortality [7]. But this method cannot appreciate calcifications' thickness and extension inside vessels. Calcification does not appear with MRI. To date, computed tomography remains the best exam as presented by Agatston in 1990 for coronary calcifications. One of this method's limits is reproducibility [22] especially for small lesions. Variability between operators is inversely proportional to the score, even if it is currently acceptable, and the new challenge is to predict cardiac events [23,24]. In this study, we hit software limits for very high calcification score above 25000 mgCaHa. This value was the maximum score given. In the future, progress will come from intravascular imaging [25,26].

Calcifications and prognosis:

Another key point concerns elderly patients. They represent a growing part of population in dialysis and on waiting list. Concerning outcomes for kidney transplantation in the elderly, mean age in our cohort is 65.3 years old in the 3rd quartile and 64.46 in the 4th one. This means 50 patients respectively followed for 4.05 and 3.83 years. Patients and grafts survival were respectively 94% and 88% at 4 years. Other older series demonstrate a lower patient and graft survival rate in elderly patients [27,28]. Our results are in line with series recently published in 2013 in elderly patients [29] [30]. Usually main causes of graft loss in older groups are death with functioning graft. Mainly deaths are caused by cardiovascular events. This confirms our previous findings: the need of a frequent and carefully complete cardiovascular follow-up.

Conclusion:

During the last decades, the main changes in Kidney transplant recipient's concerns ages and calcified aortoiliac disease. Those aortoiliac calcifications do not decrease patients and grafts survival. High calcium score predict cardiovascular events and procedures during the follow-up. This must be confirmed by more extended studies in the future.

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Disclosure: Nothing to disclose

Abbreviations:

Aortic Valve Replacement AVR
Computed Tomography CT
Coronary Artery Bypass Grafting CABG
Follow-Up FU
Glomerular Filtration Rate GFR
Hounsfield Unit HU
Kidney Transplantation KT
New Onset Diabetes After kidney Transplantation NODAT

Mitral Valve Replacement MVR

Modification of Diet in Renal Disease MDRD

Panel Reactive Antibody PRA

Percutaneous Transluminal Coronary Angioplasty PTCA

Receiver Operating Characteristic ROC

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Table 1: Patients demographics and clinical characteristics

	Cohort (n=100)	1st Quartile (n=25)	2nd Quartile (n=25)	3rd Quartile (n=25)	4th Quartile (n=25)	P-value
Global Calcium Score In mgCaHa (Mean ±SD)	8380 (±9300)	184 (±237)	2050 (±928)	8219 (±3063)	23068 (±3165)	
Demographic data						
Mean age (year)	60,3 (±12,83)	48,89	62,39	65,31	64,46	**<0.001**
Gender (% men)	67	15 (60%)	13 (52%)	19 (76%)	20 (80%)	0.08
Follow-up (median in months)	54,54	54,15	49,41	54,94	54,94	
Nephrological criteria						
Chronic Kidney Diseases						0.11
- *Glomerulonephritis*	33	7 (28%)	7 (28%)	12 (48%)	7 (28%)	
- *Hereditary nephropathy*	19	7 (28%)	6 (24%)	4 (16%)	2 (8%)	
- *Interstitial nephropathy*	9	3 (12%)	3 (12%)	1 (4%)	2 (8%)	
- *Urinary tract abnormalities*	10	5 (20%)	3 (12%)	2 (8%)	0	
- *Diabetic glomerulopathy*	10	2 (8%)	2 (8%)	2 (8%)	4 (16%)	
- *Unknown*	10	1 (4%)	3 (12%)	4 (16%)	2 (8%)	
- *Nephroangiosclerosis*	9	0	2 (8%)	1 (4%)	6 (24%)	
Mean PRA (%)	25,41 (±38,3)	17.5	30.69	19.125	34.2	0.33
Mean dialysis duration	5,93 (±7,89)	2,83	4,76	6,78	9,70	**0.046**
Cardio-Vascular risk						
Hypertension	63	15	15	17	16	NS
Tobacco	56/86 (65%)	9/22 (41%)	13/22 (60%)	14/18 (77%)	20/24 (83%)	**0.015**
Diabetes						
- *Before KT*	19	1 (4%)	9 (36%)	4 (16%)	5 (20%)	0.32
- *NODAT*	32	5 (20%)	10 (40%)	6 (24%)	11 (44%)	0.20
Dyslipidemia:						
- *Before KT*	34	6 (24%)	5 (20%)	13 (52%)	10 (40%)	0.07
- *After KT*	51	6 (24%)	13 (52%)	16 (64%)	16 (64%)	**0.01**
Pre-Transplant CV morbidity						
- Myocardial infarction	3	0	2	1	0	0.79
- PTCA and stenting	8	0	3	2	3	0.20
- CABG	2	0	0	1	1	0.26
- Ejection fraction (mean)	63.4	63.9	62.9	61.8	65.4	0.26
- Carotid endarterectomy	2	0	1	1	0	1
Total Cardiovascular disease	27	2 (8%)	7 (28%)	7 (28%)	11 (44%)	**0.03**
- Coronaropathy	16	1 (4%)	5 (20%)	5 (20%)	5 (20%)	0.26
- Peripheral arterial disease	11	1 (4%)	2 (8%)	2 (8%)	6 (24%)	0.20
Surgical data						
Cold ischemia time (hours)	22,34 (±7,3)	25,93	20,17	20,25	23,02	0.36
Warm ischemia time (min)	34,46 (±16,39)	33,92	33,20	34,76	35,96	0.94
Iliac position	78/97 (80%)	19/23 (82%)	22 (88%)	16 (64%)	21/24 (87,5%)	0.15
First Kidney Transplantation	78	23 (92%)	20 (80%)	17 (68%)	18 (72%)	0.17

KT: Kidney Transplantation
NODAT: New Onset Diabetes After kidney Transplantation
PRA: Panel Reactive Antibodies
PTCA: Percutaneous Transluminal Coronary Angioplasty
CABG: Coronary Artery Bypass Grafting

Table 2: Glomerular Filtration Rate (GFR) decay for each group between first year post transplantation and last follow-up.

	Cohort	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	P-value
Mean GFR at 1 year of Follow up: (ml/min/1.73m²)	55,0 (±22,3)	60,6	56,1	50,1	53,3	0,4
Mean GFR at last Follow up: (ml/min/1.73m²)	47,1 (±21,6)	50,7	47,5	47,9	42,2	0,57
Mean Follow up in years	4,18 (±1,64)	4,49	4,35	4,05	3,83	
GFR decrease > 10 ml/min/1.73m² (%)	23	**7 (28)**	**3 (12)**	**5 (20)**	**8 (32)**	0,36
GFR's slope (ml/min/1.73m² /year)	-2,21 (±5,71)	**-2,05**	**-3,51**	**-0,77**	**-2,59**	0,4

Table 3: Number of post-transplantation cardiovascular procedures

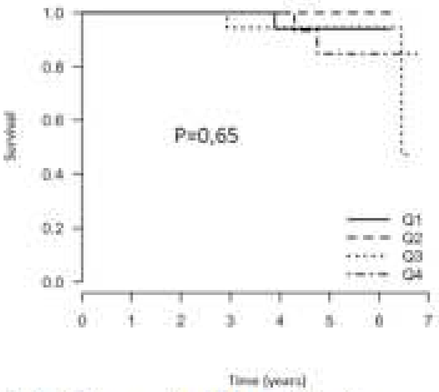
Procedures	Cohort	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile
Cardiac:					
- **Number**	4	0	1	2	1
- **Type**			Coronary stenting	AVR+MVR AVR	Coronary stenting
Vascular:					
- **Number**	8	0	1	2	5
- **Type**			Peripheral angioplasty	Carotid endarterectomy	4 peripheral stenting 1 bypass
Graft artery:					
- **Number**	6	0	2	2	2
- **Type**			Angioplasty	Angioplasty	1 bypass 1 angioplasty
Total	18/100	0/25	4/25	6/25	8/25

AVR: Aortic valve replacement

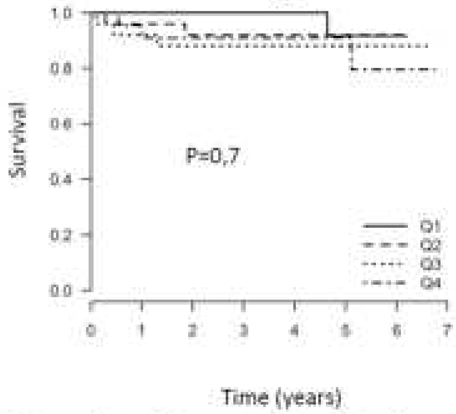
MVR: Mitral Valve replacement

Figure 1 Kaplan Meyer survival curves:

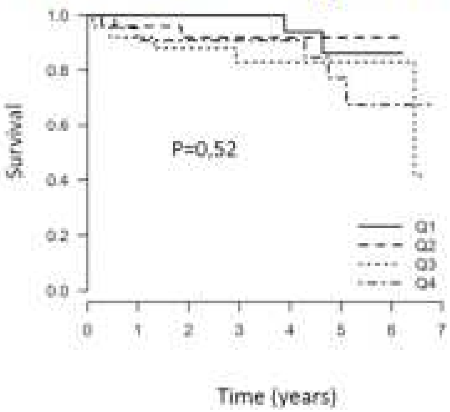
1A. Patient's survival for global score.



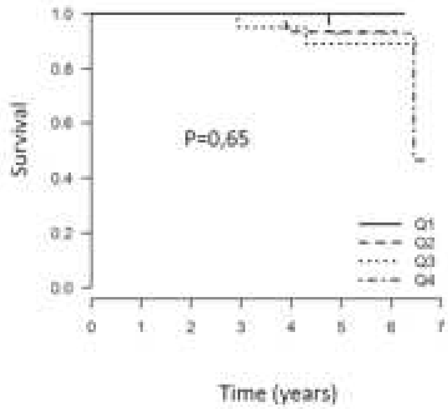
1B. Graft's survival for global score.



1C. Combined Survival for global score.



1D. Patient's survival for selective score.



1E. Graft's survival for selective score.

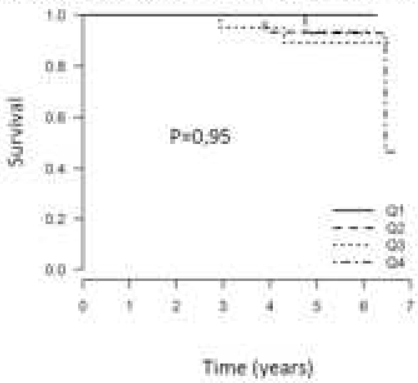


Figure 2: ROC curves

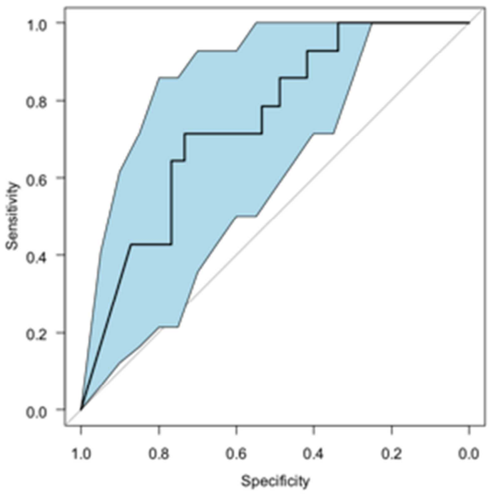


Fig 2A: ROC curve – global score

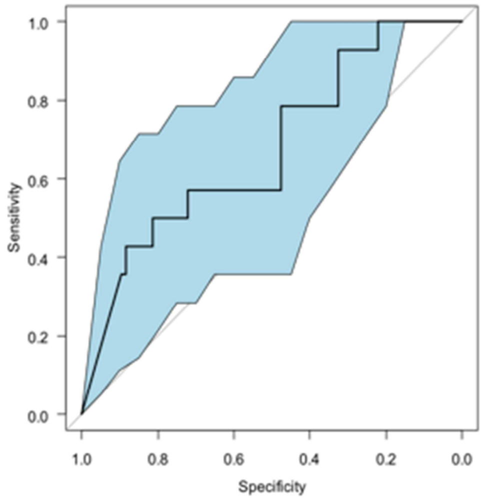


Fig 2B: ROC curve – Selective score