# SERUM ASYMMETRIC DIMETHYLARGININE IS RELATED TO HEMODIALYSIS MORTALITY IN NON DIABETIC INDIVIDUALS

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## OBJECTIVES

ADMA, the principal endogenous nitric oxide synthase inhibitor, is substantially increased in plasma of patients on Hemodialysis (HD), and may either works as a biomarker of HD mortality or be causally related. We aimed to evaluate the association of ADMA levels with HD mortality in an observational prospective study.

## METHODS

Predialysis ADMA levels have been measured by HPLC in 202 individuals prevalents on HD. Their association with all-cause mortality over a 4 years period was analyzed using a Cox model adjusted for potential confounders (demographics, clinical characteristics, comorbidities, albumin, PTH, CRP). Statistics through IBM SPSS Statistics 20,0.

## RESULTS

TABLE 1 depicts demographic, clinical and laboratory characteristics of patients of the whole group. Diabetics were older (57,1 ± 13,3 vs 50,2 ± 15,1 years, P = 0,002 Student test), heavier (BMI: 25,9 ± 2,9 vs 24,9 ± 2,4, P = 0,017 Student t test), and had a greater prevalence of coronary disease (36,9% vs 15,0%, P = 0,001 Chi square). Median (interquartile range) for ADMA was 1.71 µM (0,60, 1.37) in diabetics vs 0.88 µM (0.23, 2,25) in non diabetics (P = 0.059 Mann Whitney). Death occurred in 41 (20,3%) and 40 (19,8%) received a graft. TABLE 2 depicts demographic, clinical and laboratory patients characteristics according to evolution. In fully adjusted models, ADMA was associated with mortality in non diabetics, but not in diabetics (P = 0,000, HR: 2,294, 95% CI: 1,63 3,22). (GRAPHIC 1) The area under the ROC curve provided by ADMA in non diabetics was 0.858 (P = 0.000, 95% CI: 0.790 - 0.926). (GRAPHIC 2). There was no correlation between ADMA and CRP.
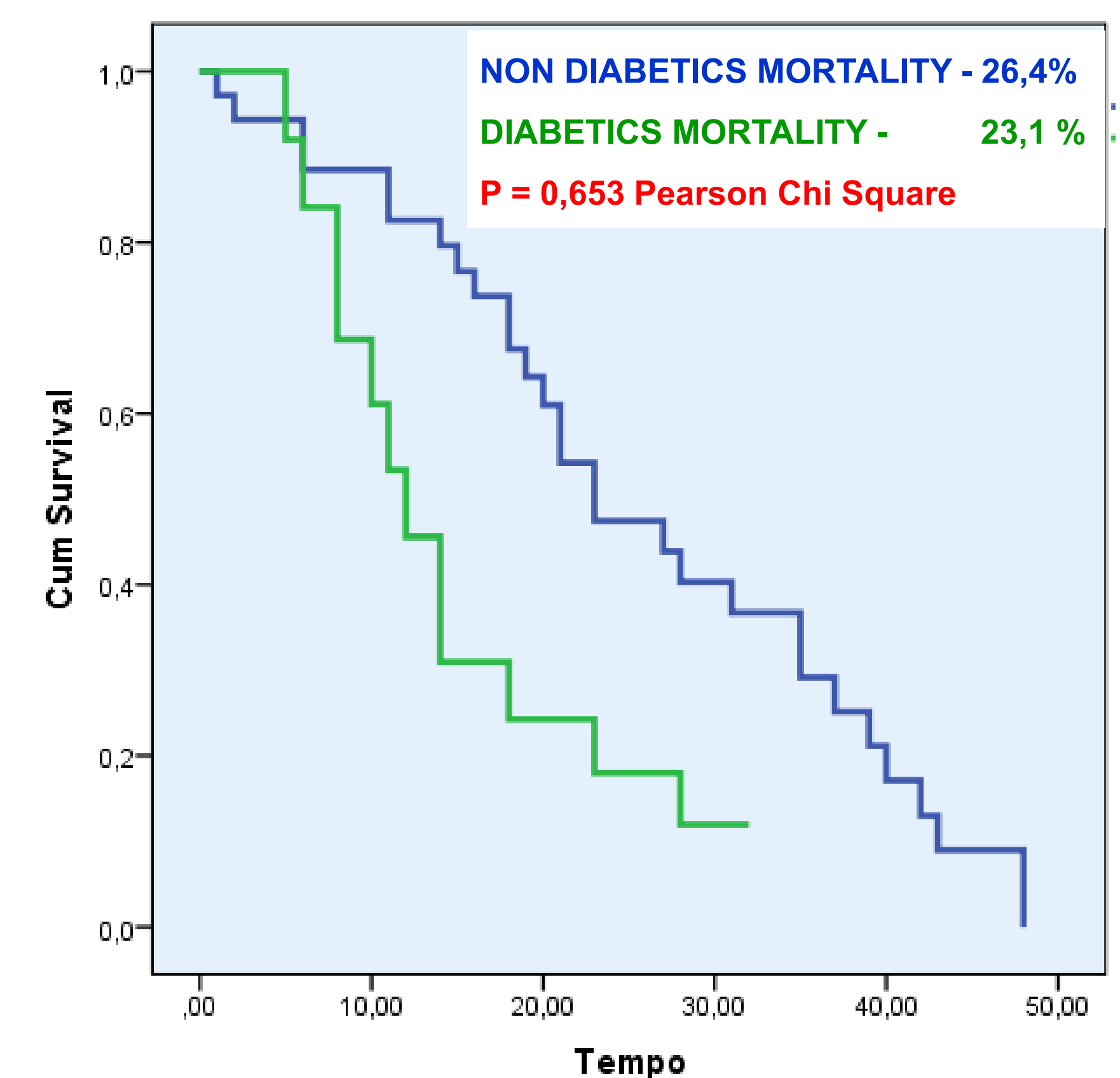
### TABLE 1: Demographic, clinical and laboratory characteristics of patients.

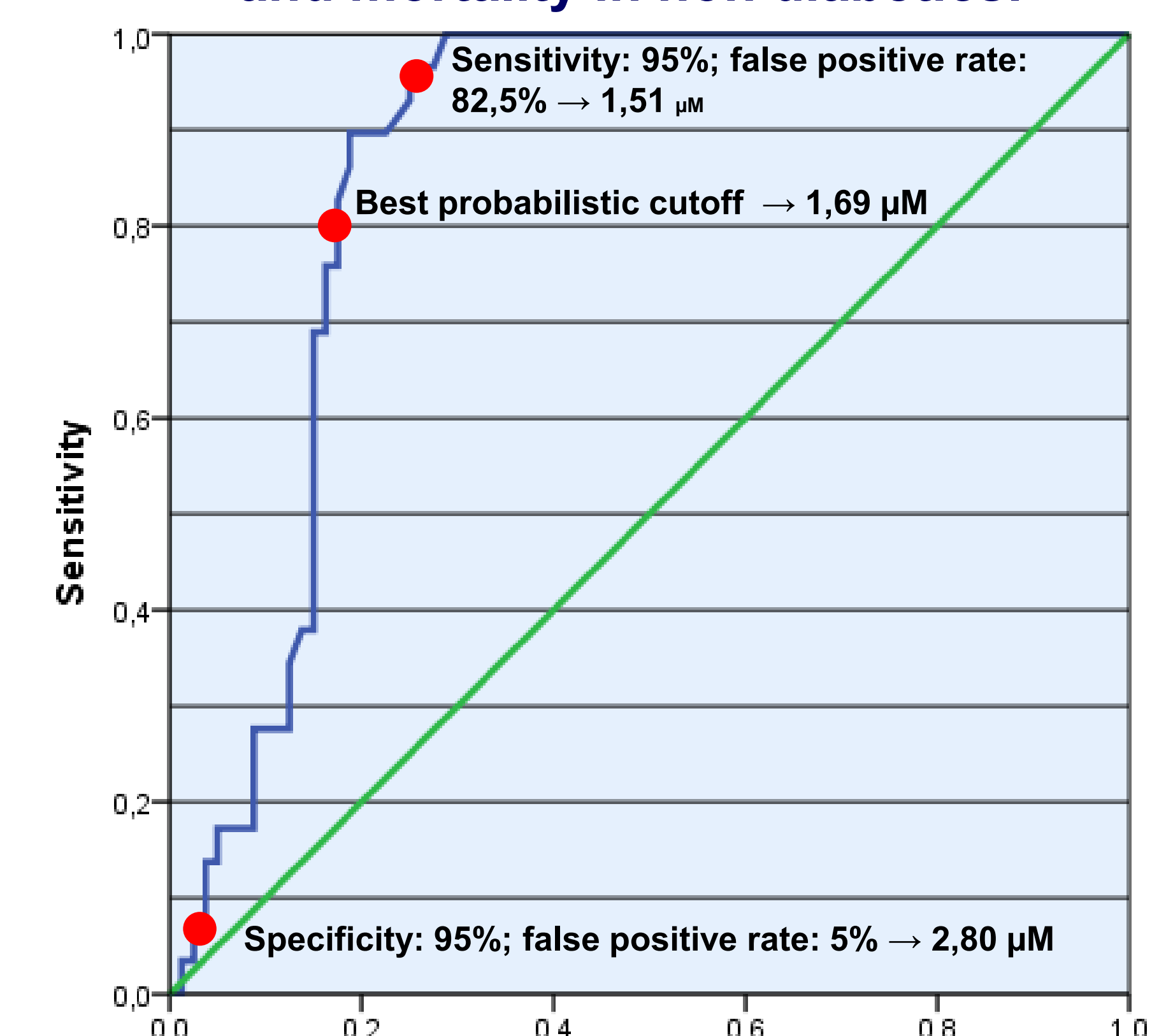| | Total (N = 202) |
|---|---|
| Age (years) | 52,5 ± 14,9 |
| Male | 118 (58,4%) |
| Dialysis vintage (months) | 37,2 ± 26,9 |
| Caucasian | 138 (68,3%) |
| BMI (kg/cm$^2$) | 25,2 ± 2,6 |
| Waist circumference (cm) | 97,8 ± 11,0 |
| Diabetes mellitus | 136 (67,3%) |
| Hypertension | 179 (88,6%) |
| Cardiovascular Disease | 86 (42,6%) |
| o Cerebrovascular disease | 21 (10,4%) |
| o Coronary disease | 44 (21,8%) |
| o Peripheral vascular disease | 46 (22,8%) |
| o Congestive heart failure | 31 (15,3%) |
| Renin angiotensin system inhibitors use | 140 (69,3%) |
| Statin use | 108 (53,5%) |
| Acetylsalicylic Acid use | 73 (36,1%) |
| HDL-C (mg/dL) | 38,2 ± 14,4 |
| LDL-C (mg/dL) | 73,0 ± 28,7 |
| Triglycerides (mg/dL) | 169,4 ± 116,1 |
| Albumin (mg/dL) | 3,8 ± 0,3 |
| PTH (pg/ml) | 413,0 ± 355,0 |
| ADMA (µM) – median (IQR) | 1,28 (0,89, 1,91) |
| CRP (mg/dL) _ median (IQR) | 0,39 (0,15 1,18) |

### TABLE 2: Demographic, clinical and laboratory characteristics of patients according to evolution. (*Student t test, **Mann Whitney U test, ***Chi Square)

| | Alived (N = 121) | Death (N = 41) | P |
|---|---|---|---|
| Age (years) | 53,4 ± 15,4 | 56,8 ± 13,4 | 0,214* |
| Male | 71 (58,7%) | 23 (56,1%) | 0,772*** |
| Dialysis vintage (months) | 55,6 ± 22,7 | 41,8 ± 31,8 | 0,190* |
| Caucasian | 79 (65,3%) | 33 (80,5%) | 0,187*** |
| BMI (kg/cm$^2$) | 25,3 ± 2,6 | 25,8 ± 2,8 | 0,270* |
| Waist circumference (cm) | 98,2 ± 11,1 | 98,5 ± 9,8 | 0,873* |
| Diabetes mellitus | 40 (33,1%) | 12 (29,3%) | 0,653*** |
| Hypertension | 107 (88,4%) | 38 (92,7%) | 0,443*** |
| Cardiovascular Disease | 53 (44,2%) | 20 (51,3%) | 0,439*** |
| o Cerebrovascular disease | 11 (11,2%) | 07 (12,0%) | 0,133*** |
| o Coronary disease | 24 (20,0%) | 12 (30,8%) | 0,163*** |
| o Peripheral vascular disease | 28(23,3%) | 09 (23,1%) | 0,974*** |
| o Congestive heart failure | 23 (19,2%) | 05 (12,8%) | 0,366*** |
| Renin angiotensin system inhibitors use | 87 (72,5%) | 29 (70,7 %) | 0,828*** |
| Statin use | 61 (50,8%) | 25 (61,0%) | 0,261*** |
| Acetylsalicylic Acid use | 42 (34,7%) | 15 (36,6%) | 0,828*** |
| HDL-C (mg/dL) | 38,7 ± 15,6 | 37,7 ± 13,4 | 0,693* |
| LDL-C (mg/dL) | 74,3 ± 30,9 | 75,4 ± 26,9 | 0,841* |
| Triglycerides (mg/dL) | 168,4 ± 125,5 | 156,8 ± 75,1 | 0,579* |
| Albumin (mg/dL) | 3,8 ± 0,3 | 3,8 ± 0,3 | 0,741* |
| PTH (pg/ml) | 410,0 ± 349,3 | 403,9 ± 373,1 | 0,924* |
| ADMA (µM) – median (IQR) | 0,88 (0,60, 1,37) | 1,71 (1,34, 2,17) | 0,000** |
| CRP (mg/dL) _ median (IQR) | 0,38 (0,15, 1,18) | 0,77 (0,23, 2,25) | 0,034** |

### GRAPHIC 1: Cox regression curves for survival according to diabetic status



NON DIABETICS MORTALITY - 26,4%
DIABETICS MORTALITY - 23,1 %
P = 0,653 Pearson Chi Square

### GRAPHIC 2: ROC curve for ADMA and mortality in non diabetics.



Sensitivity: 95%; false positive rate: 82,5% → 1,51 µM
Best probabilistic cutoff → 1,69 µM
Specificity: 95%; false positive rate: 5% → 2,80 µM

## CONCLUSIONS

ADMA may be use as a biomarker of mortality risk into HD non diabetic patients, but with low specificity. Previous works had not cited differences between diabetics and non diabetics, neither had made analysis about sensibility and specificity.[1,2] In one of these works the diabetics prevalence was 15%.[1] It is possible that other risk factors for mortality in HD overlap ADMA among diabetics. Or that the diabetic cohort was small.

## References

1. Inflammation and Asymmetric Dimethylarginine for predicting Death and Cardiovascular Events in ESRD patients Clin J Am Soc Nephrol 2011, 6:1714-21.
2. Serum Asymmetric (ADMA) and Symmetric (SDMA) Dimethylarginine and Morbidity and Mortality in Hemodialysis Patients: The Retained Organic Solutes and Clinical Outcomes (ROSCO) Study(Abstract). J Am Soc Nephrol 26, 2015:69A.