CAN GENETIC RISK SCORES IMPROVE THE PREDICTON POWER FOR MORTALITY OF STANDARD RISK FACTORS IN THE END STAGE KIDNEY DISEASE POPULATION?: AN EXPLORATORY STUDY

Belinda Spoto[1], Alessandra Testa[1], Graziella D'Arrigo[1], Rosa M. Parlongo[1], Maria C. Sanguedolce[1], Anna Pisano[1], Giovanni Tripepi[1], Carmine Zoccali[1], Francesca Mallamaci[1,2]

[1]CNR-IFC, Clinical Epidemiology and Physiopathology of Renal Diseases and Hypertension, Reggio Calabria, ITALY, [2]Riuniti Hospital, Nephrology and Renal Transplantation Unit, Reggio Calabria, ITALY.

Introduction and aims

In large studies in the general population, combinations of genetic polymorphisms (genetic risk scores, GRS) improve the prediction power of classical risk factors for all-cause and cardiovascular mortality. ESKD patients maintained on chronic dialysis have an exceedingly high risk for mortality and an almost unique risk profile characterized by inverse epidemiology, competing risk factors and population selection. Recently a risk score (RS) for mortality in ESKD has been extensively validated in diverse populations (Kidney Int. 2015;87:996-1008). Whether the application of genetic risk scores in ESKD may improve the prognostic power of simple risk prediction instruments, like the RS, has never been explored.

Methods

The test population was a cohort of 188 hemodialysis patients (age 59±15, 105/83 M/F) followed up for a median time of 3.9 years. We genotyped 124 single nucleotide polymorphisms (SNP) or insertion/deletion polymorphisms in 54 genes which have been reported to be associated with mortality in ESKF patients and/or in high risk conditions (such as diabetes and cardiovascular diseases). Among these polymorphisms, 4 SNPs [rs708259 (FTO); rs1047214 (NPY2R); rs4807546 (SIRT6); rs1044498 (ENPP1)] at four independent loci resulted to be significantly associated with all-cause mortality in our cohort. As an index of global genetic burden, we calculated a weighted GRS by summing up the number of risk alleles recoded in rank order.

Genes	Polymorphism
FTO	rs708259
NPY2R	rs1047214
SIRT6	rs4807546
ENPP1	rs1044498

Results

Both the RS (median 3, IQR: -1-6) and GRS (median 0.6, IQR: 0.3-0.8) had a non-normal distribution and tended to be inter-related (rho 0.12, P=0.09).

During the follow-up period, 129 patients died (40% of cardiovascular causes). On univariate Cox regression analyses, the RS significantly predicted mortality [hazard ratio (1 unit increase): 1.13, 95% CI: 1.08-1.18, P<0.001] and this was also true for the GRS [hazard ratio (1 unit increase): 2.29, 95% CI: 1.40-3.75, P=0.001]. The RS-based model (basic model) provided a discriminatory power for distinguishing patients who died from those who survived of 65% and an explained variation in mortality (an index combining discrimination and calibration) of 27%. When GRS was added into the basic model, both risk scores [RS, HR: 1.12, 95% CI: 1.07-1.17, P<0.001; GRS, HR: 1.80, 95% CI: 1.10-2.95, P=0.02] significantly predicted mortality. The inclusion of GRS improved (P<0.02) discrimination (from 65% to 66%), calibration (χ^2 from 2.79 to 2.32) and explained variation in mortality (from 27% to 31%) of the basic model. Of note, GRS produced a NRI of 15% and an IDI of 3% (P=0.03 and P=0.02, respectively).

p≤0,001

Hazard ratio and 95% CI — RS, GRS
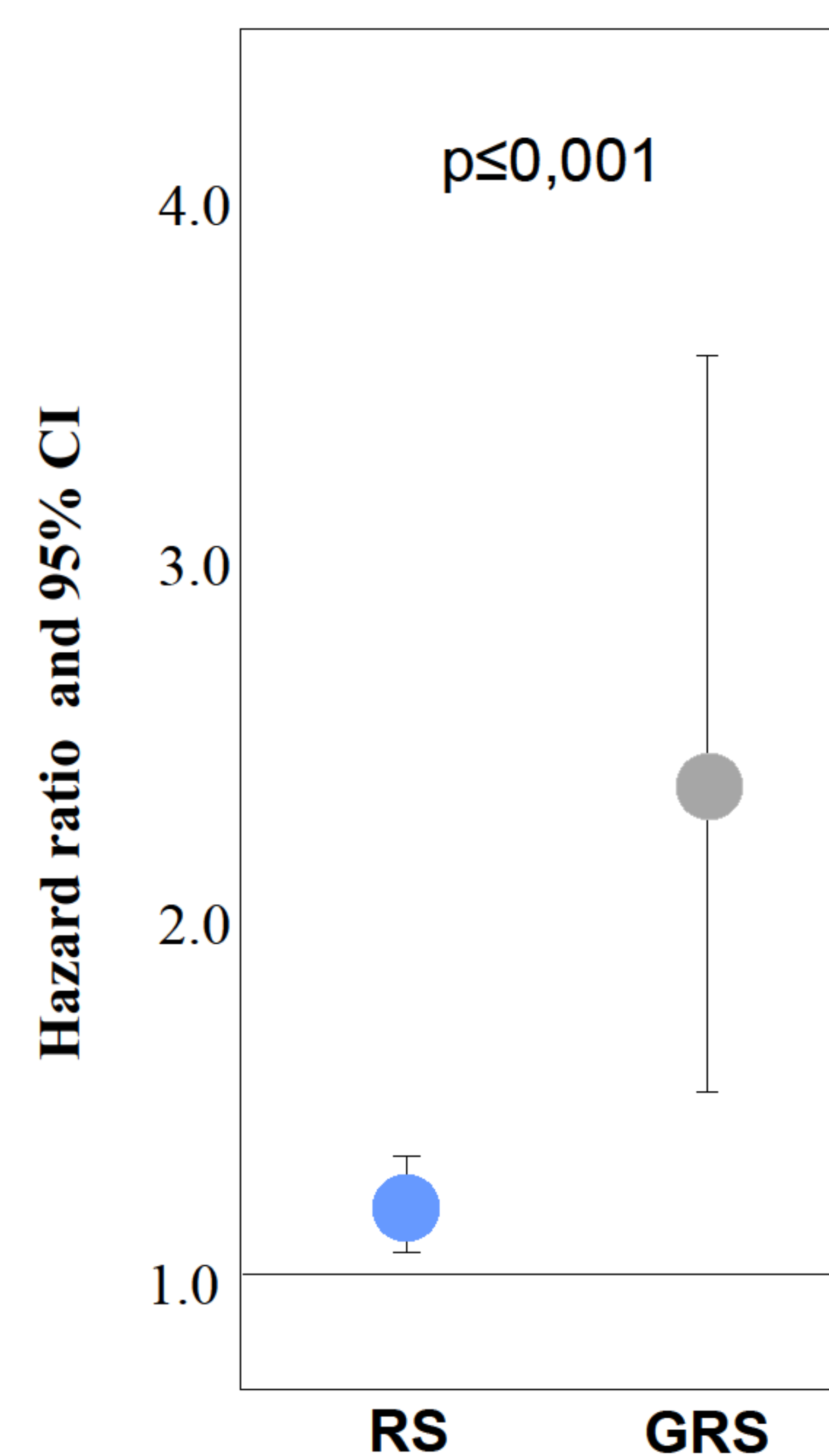
Conclusions

A genetic risk score composed of four genetic polymorphisms refines the prediction power for mortality of a well-validated risk score in the hemodialysis population. Replication studies in larger cohorts are needed to establish the validity of the genetic risk score in the test cohort of the present study.

These data represent proof of concept of the potential value of genetic risk scores for refining prognosis in the dialysis population.