Supplementary Methods and Figures

Clonal myelopoiesis promotes adverse outcomes in chronic kidney disease

Ahmed A.Z. Dawoud, Rodney D. Gilbert, William J Tapper & Nicholas C.P. Cross

Supplementary Methods

Identification of clonal hematopoiesis from WES data

To identify putative somatic driver mutations from WES data, individual gVCF files from the DeepVariant version 0.10.0 caller[1] were converted to VCF format and merged into one multi-sample VCF using SAMtools/Bcftools[2]. Multi-allelic variants were split into separate variants and the location of indels was normalised using their left most position.[3] The multisample VCF was annotated using Annovar and the RefSeq gene database.[4] Variants were defined as putative somatic driver mutations if they met the following criteria; (i) exonic, or splice donor/acceptor site; (ii) the alternative allele had a minimum of 3 reads for point mutation and 6 reads for indels; (iii) alternate allele frequency ≤1% in GnomAD V2.1;[5] (iv) predicted to be pathogenic (CADD[6] phred score >20 meaning that the variant is among the 1% most deleterious variants in the human genome); (v) minor allele frequency (MAF) ≤ 0.01% in UKB; (vi) observed in COSMIC version 91 database[7] at least 3 times in hematopoietic and lymphoid tissues; (vii) inferred as somatic by failing the hypothesis that the alternative allele is normally distributed with a mean of 0.45 and a false positive rate of P=0.05 using a binomial test as described.[8] Several exceptions to the rules to define putative somatic driver mutations were made in order to capture all relevant variants in known driver genes: (i) MAF >0.01 in UKB for *DNMT3A* R882, *JAK2* V617F and *GNB1* K57E; (ii) *TP53*: all mutations seen in at least once in COSMIC and validated in the International Agency for Research on Cancer database[9] were included (iii) *TET2*: all missense mutations were included in regions encoding the catalytic domains (amino acids 1104-1481 and 1843- 2002)[10; 11]; (iv) any *DNMT3A* variant was included that was seen at least once in COSMIC; (v) all frameshift indels, stopgain, and splice site mutations listed in a list of known myeloid neoplasia related genes were included[12].

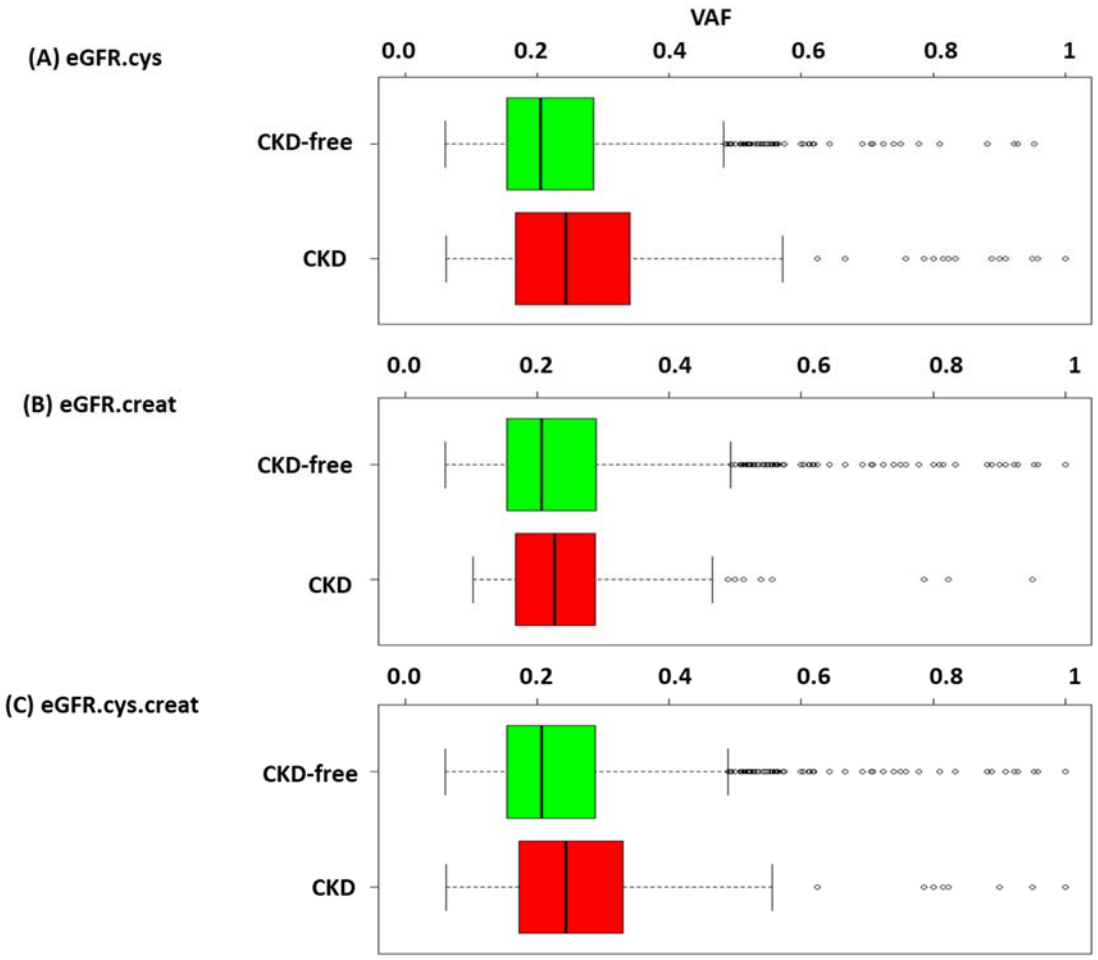
Exceptions to the binomial test were made for established driver variants with high fitness, e.g. *U2AF1* Q157, *FLT3* Y842C, *JAK3* R657Q, *IDH2* R140L, *CBL* Y371H, and *KRAS* G12V due to the high fitness of these variants.[13] Variants that were absent from COSMIC were only considered if they had a heterozygous "0/1" or homozygous "1/1" genotype indicative of high quality genotype calls.

Diagnosis of ESKD

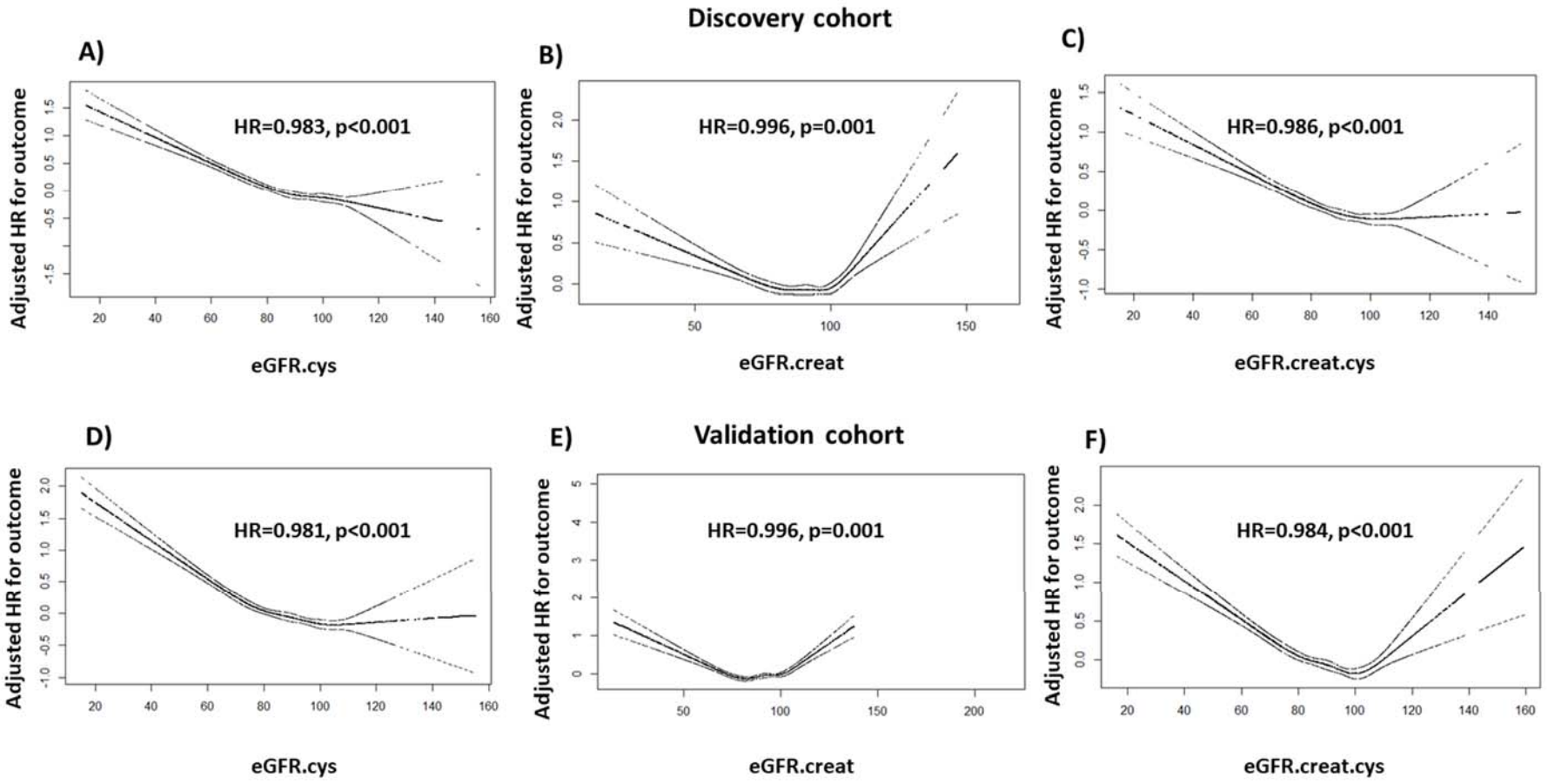
ICD10 codes used to classify ESKD in UKB participants were E85.3, N16.5, N18.0, N18.5, Q60.1, T82.4, T86.1, Y60.2, Y61.2, Y62.2, Y84.1, Z49.0, Z49.1, Z49.2, Z94.0, Z99.2. ESKD was also inferred by relevant interventions and procedures (OPCS4: L74.1, L74.2, L74.3, L74.4, L74.5, L74.6, L74.8, L74.9, M01.2, M01.3, M01.4, M01.5, M01.8, M01.9, M02.3, M08.4, M17.2, M17.4, M17.8, M17.9, X40.1, X40.2, X40.3, X40.4, X40.5, X40.6, X40.7, X40.8, X40.9, X41.1, X41.2, X41.8, X41.9, X42.1, X42.8, X42.9, X43.1)[14]

Prevalent and incident myeloid neoplasia

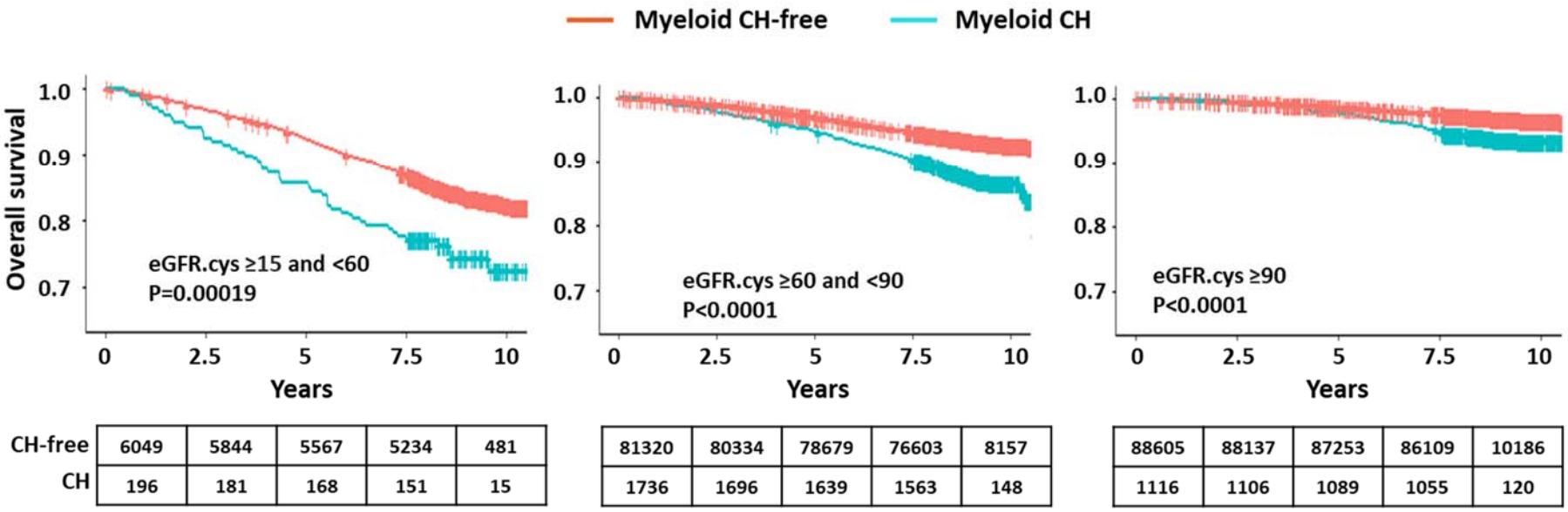
Participants with myeloid malignancy were identified from the national cancer registry and hospital inpatient records using the ICD10 codes C920, C921, C923, C924, C925, C927, C929, C930, C931, C940, C944, C946, C962, D45, D460, D461, D462, D464, D467, D469, D470, D471 and D473. Myeloid malignancies were considered prevalent if diagnosed before or within one year of study (n=320) entry, or incident (n=419) if diagnosed a year or more after study entry. The relationship between CH and ESKD in the absence of prevalent myeloid neoplasia was tested using multivariable logistic regression in R where ESKD diagnosed after the study entry was used as the dependant and CH as a binary predictor, and adjusted for the same CKD risk factors.



Supplementary Figure 1: CKD, defined by eGFR <60, is associated with VAF of driver mutations in myeloid related genes in 3,328 participants. Meta-analysis of discovery and validation cohorts (A) eGFR.cys: CKD (n=293), median = 0.24; CKD-free (n=3,035), median = 0.21 (P = 1.71×10^{-7}; Mann-Whitney test), (B) eGFR.creat: CKD (n=111), median = 0.23; CKD-free (n= 3,217), median = 0.21 (P=0.12), (C) eGFR.creat.cys: CKD (n=144), median=0.23; CKD-free (n=3,184), median= 0.21 (P = 0.0002).



Supplementary Figure 2: Restricted cubic spline to test the linearity of eGFR scores. Adjusted spline of each eGFR score was plotted against HR for outcome with default values for the number of knots (n=5) and degrees of freedom (n=4). The upper and the lower dotted lines indicate 95% confidence intervals. A, B, and C refer to the discovery cohort. D, E, and F refer to the validation cohort for each eGFR score.



Supplementary Figure 3: Kaplan-Meier survival estimates for the three CKD groups according to absence or presence of myeloid CH, and excluding the 966 participants with potential SPS. Log-rank test P values are reported for each group, and numbers at risk at 0, 2.5, 5, 7.5, and 10 years after study entry.

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