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Human Kinetics
LETTER TO THE EDITOR

A Comment on González et al: Predicting Injuries in Elite Female Football Players With Global-Positioning-System and Multiomics Data

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Investigating health prognosis revolves around predicting or estimating the probability or risk of patients or athletes developing illness states, or experiencing certain events over a specific time given their clinical and nonclinical characteristics.[1] The recent study by González et al[2] examined the predictive value of Global-Positioning-System and multiomics data for noncontact injury occurrence in 24 female football players. Considering the fundamental design issues of this study,[2] which are common to similar investigations in other clinical realms,[3] prognostic models developed with an inadequate sample size yield unstable predictions as potential artifacts of data sparsity[4] that can mislead decisions for some individuals and may have the potential to cause harm.[5,6] With this in mind, and although it was concluded the estimated "model could allow efficient, personalized interventions based on an athlete's vulnerability" (p 661), here design analyses reveal how findings arising from small-scale studies can be misleading and what might happen in future studies of similar size.[7]

Table 1 Type M Error Rate, Type S Error Risk, and Corrected Probabilities of Injury-Free Survival Across True Prognostic Effects by Genomic Variable

Genomic variable	True prognostic effect	Type M error[a]	Type S error (%)[b]	Corrected HR (95% CI)[c]	Probabilistic index (95% CI)[d]
rs1799750	HR = 0.90	6.0	13.5	0.88 (0.81–0.97)	0.53 (0.51–0.55)
	HR = 0.80	2.9	1.9	0.77 (0.65–0.93)	0.57 (0.52–0.60)
	HR = 0.70	1.9	0.2	0.67 (0.52–0.90)	0.60 (0.53–0.66)
rs699947	HR = 0.90	7.6	18.9	0.91 (0.83–0.99)	0.52 (0.50–0.55)
	HR = 0.80	3.7	4.3	0.82 (0.68–0.98)	0.55 (0.50–0.59)
	HR = 0.70	2.4	0.7	0.74 (0.56–0.97)	0.57 (0.51–0.64)
rs9406328	HR = 0.90	8.0	20.2	0.91 (0.83–0.99)	0.52 (0.50–0.55)
	HR = 0.80	3.9	5.2	0.82 (0.68–0.98)	0.55 (0.50–0.59)
	HR = 0.70	2.5	0.9	0.73 (0.56–0.98)	0.58 (0.51–0.64)
rs162502	HR = 0.90	10.5	26.0	0.93 (0.87–0.99)	0.52 (0.50–0.54)
	HR = 0.80	5.0	9.8	0.86 (0.75–0.99)	0.54 (0.50–0.57)
	HR = 0.70	3.2	2.8	0.78 (0.63–0.98)	0.56 (0.51–0.61)
rs4903399	HR = 0.90	10.1	25.0	0.90 (0.82–0.98)	0.53 (0.51–0.55)
	HR = 0.80	4.8	8.8	0.80 (0.66–0.96)	0.56 (0.51–0.60)
	HR = 0.70	3.1	2.3	0.70 (0.53–0.93)	0.59 (0.52–0.66)
rs516115[e]	HR = 0.90	4.5	7.6	0.91 (0.83–0.99)	0.52 (0.50–0.55)
	HR = 0.80	2.2	0.5	0.82 (0.69–0.97)	0.55 (0.51–0.59)
	HR = 0.70	1.5	0.0	0.74 (0.57–0.96)	0.57 (0.51–0.64)

Abbreviation: HR, hazard ratio.
[a]The degree of overestimation of an observed effect estimate relative to the magnitude of the true population effect given a study design.[7,8] [b]The probability that a statistically significant injury-free survival estimate is in the wrong direction compared to the true prognostic effect.[7,8] [c]Corrected HR derived by dividing the natural logarithm of the estimated HR by the respective magnitude of exaggeration or type M error rate relative to the target true prognostic effect.[7] [d]The probability, calculated as $1/[1 + HR]$,[9] that the injury-free survival period was longer for athlete$_j$ with a rare allele expression compared to athlete$_i$ with a normal genotype. This reanalysis formula includes the corrected HR as an illustrative example.[7] [e]The correct 95% CI for the observed HR of 0.64 in the original report[2] should have ranged from 0.43 to 0.94 given the exact P value of .0235 according to the procedures illustrated in Altman and Bland.[10]

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First, adopting the methodological framework illustrated by Lord et al[8] and using the *retrodesign()* function,[7] design calculations estimated the probability that a statistically significant injury-free survival estimate is in the wrong direction (type S error) and the degree of overestimation of an observed effect estimate relative to the magnitude of the true population effect (type M error) given this study design[2] across true median injury-free survival effects corresponding to target hazard ratios (HRs) of 0.90, 0.80, and 0.70 (see Supplementary Material [available online]).[7,8] Design analyses indicated that any effect observed for the rare alleles of the target polymorphisms[2] was unreliable, with up to 26% risk of claiming the presence of a rare variant is falsely protective and overestimated by approximately 10 orders of magnitude for reliably detecting a true effect as small as HR of 0.90 (Table 1).

Second, the study results' elaboration[2] might have fallen foul of general misinterpretations of HRs as alternative effect measures of absolute risk.[9] In the hypothetical absence of competing risks and correct model specification, an estimated HR can be related to the probabilistic index, calculated as $1/[1 + \mathrm{HR}]$[9] denoting the probability that the event time of athletes with a rare allele expression exceeds substantially the event time of athletes with a normal genotype resting on also other candidate predictors. For example, Table 1 illustrates that the true probability the injury-free survival period was longer for athletes with a rare allele expression compared with athletes with a normal genotype was 53% (95% CI 51%–55%) given the corrected HR of 0.88 (95% CI 0.81–0.97).

Prognostic models developed on data that are too small for unbiased and precise clinical prognostication are prone to instability[3,5,6] and should not be used to inform decisions on athlete management if unvalidated.[11] Fundamentally, it seems unreasonable to draw any conclusive inference from small-scale studies that are inconsistent with the standards required for appropriate clinical prediction model development and validation.[1,12] For future research endeavors on multivariable prognostic model development and use for any potential injury prevention purpose, the actionability of any injury risk estimation, whether clinically meaningful, rests on following available guidance for studies to meet minimum sample size and reporting requirements.[1,5,12]

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