Predicting persistent severe acute kidney injury (AKI) using the urinary C-C motif chemokine ligand 14 biomarker (CCL14): A cost-utility analysis in Spain and the UK

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Background

- Acute and chronic conditions can impair the normal functioning of the kidney and lead to acute kidney injury (AKI). Spontaneous recovery can occur, but patients progressing to more severe disease are at increased risk of systemic impairment, chronic kidney disease (CKD), and death [1,2]. AKI is very common among patients requiring intensive care, and management is resource intensive, which limits adherence to standardized care bundles [3].
- As currently there is no intervention that can effectively reverse AKI in people with moderate to severe (stage 2-3) AKI [2], clinical emphasis has been put on prevention and early identification.
- The urinary CCL14 biomarker is predictive of persistent severe AKI (PS-AKI), defined as stage 3 AKI lasting ≥3 days or leading to death within 3 days, or stage 2-3 AKI with dialysis within 3 days [4].
- Early identification of patients at risk of PS-AKI may contribute to focusing AKI management and hypothetically avoid the associated costs and health consequences. Investigating the cost-effectiveness of the CCL14 biomarker may therefore be useful to predict implementation challenges and contribute to steering future research.

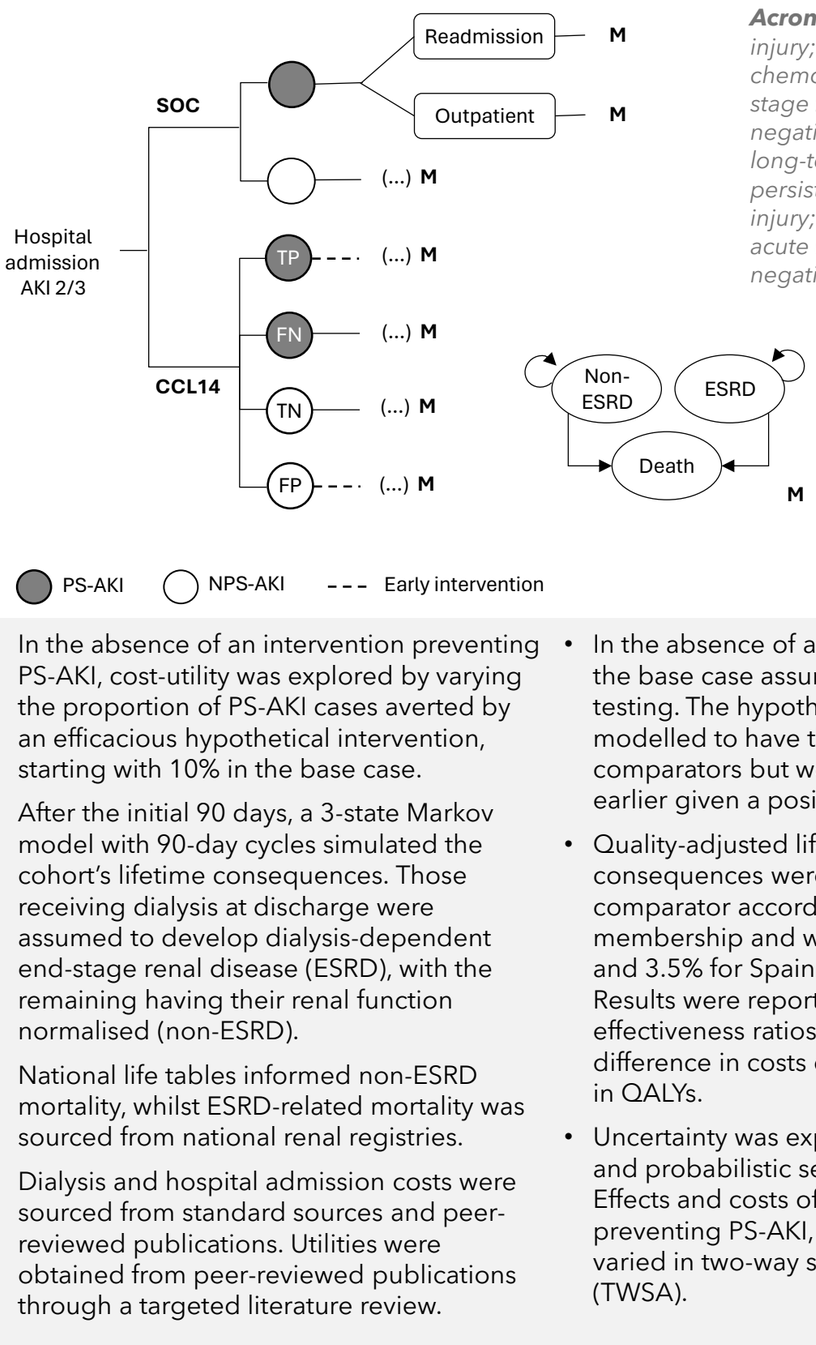
Objective

- The aim of this analysis is to explore the cost-utility of using a biomarker specific to PS-AKI, compared to standard of care (SOC) alone, in hospitalized stage 2-3 AKI patients in Spain and the UK.

Methods

- A decision tree was populated with CCL14 diagnostic operating characteristics to estimate the probability of PS-AKI and 90-day clinical outcomes in 66-year-old individuals (50% females) (Figure 1). At a threshold of 1.3 ng/ml, CCL14 sensitivity (0.91, 95% CI 0.84-0.96) informed the proportion of true positive (TP) diagnoses, CCL14 specificity (0.51,95% CI 0.44 to 0.57) the proportion of true negatives (TN) [3].
- In the absence of local data, dialysis and intensive care dialysis requirements, length of hospital stay, readmission, and 30-day mortality were sourced from the analysis of a large cohort (n=126,528) covering 20% of all US hospital admissions and reporting clinical outcomes on a subsample with PS-AKI (24.4%, n=30,916) [5].

Figure 1 *– Structure of the decision tree and Markov model*



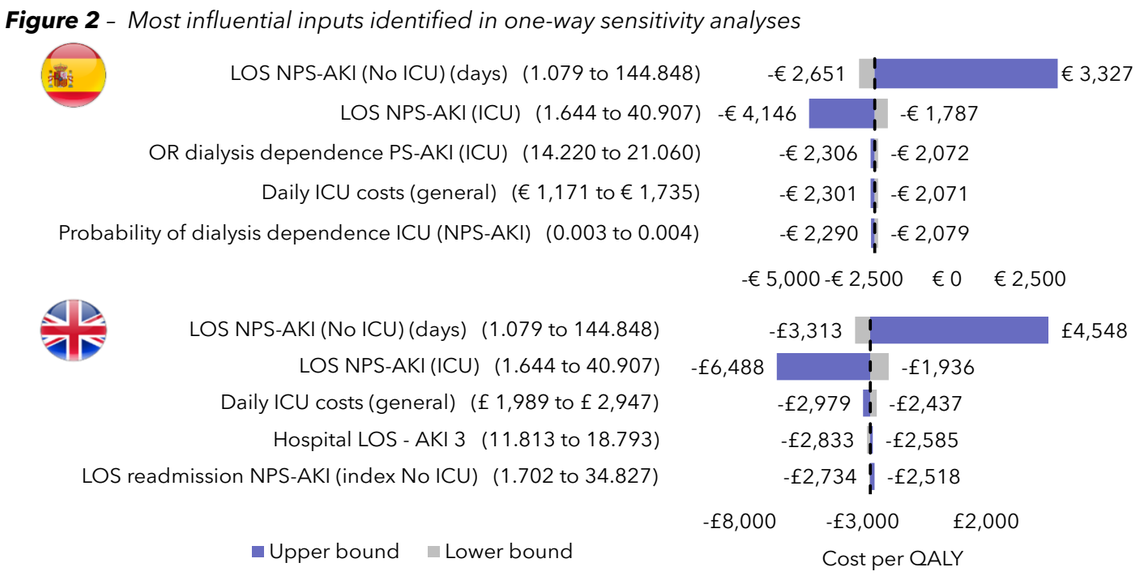
Acronyms*: AKI, acute kidney injury; CCL14, urinary C-C motif chemokine ligand 14; ESRD, end-stage renal disease; FN, false negative; FP, false positive; M, long-term Markov trace; PS-AKI, persistent severe acute kidney injury; NPS-AKI, non-persistent acute kidney injury; TN, true negative TP, true positive.*

- In the absence of an intervention preventing PS-AKI, cost-utility was explored by varying the proportion of PS-AKI cases averted by an efficacious hypothetical intervention, starting with 10% in the base case.
- After the initial 90 days, a 3-state Markov model with 90-day cycles simulated the cohort's lifetime consequences. Those receiving dialysis at discharge were assumed to develop dialysis-dependent end-stage renal disease (ESRD), with the remaining having their renal function normalised (non-ESRD).
- National life tables informed non-ESRD mortality, whilst ESRD-related mortality was sourced from national renal registries.
- Dialysis and hospital admission costs were sourced from standard sources and peer-reviewed publications. Utilities were obtained from peer-reviewed publications through a targeted literature review.
- In the absence of a market price for CCL14, the base case assumes no additional cost for testing. The hypothetical intervention was modelled to have the same cost for both comparators but would be implemented earlier given a positive test.
- Quality-adjusted life years (QALYs) and cost-consequences were accrued for each comparator according to health state membership and were discounted at 3% and 3.5% for Spain and the UK, respectively. Results were reported as incremental cost-effectiveness ratios (ICER), calculated as the difference in costs divided by the difference in QALYs.
- Uncertainty was explored in deterministic and probabilistic sensitivity analyses (PSA). Effects and costs of an intervention preventing PS-AKI, and testing costs were varied in two-way sensitivity analyses (TWSA).

Results

- By preventing PS-AKI in as few as 10% of TP cases, a CCL14-informed clinical practice resulted in QALYs gain in both countries. CCL14 was associated with lower costs (dominating) and a high probability of being cost-effective at the €30,000/QALY and £20,000/QALY thresholds (Table 1).
- CCL14 remained cost-effective after including testing (€/£400) and intervention costs (€/£1,000). Additional scenarios did not change the conclusions.
- Inputs related to the duration of the intensive care admission were the most influential (Figure 2).

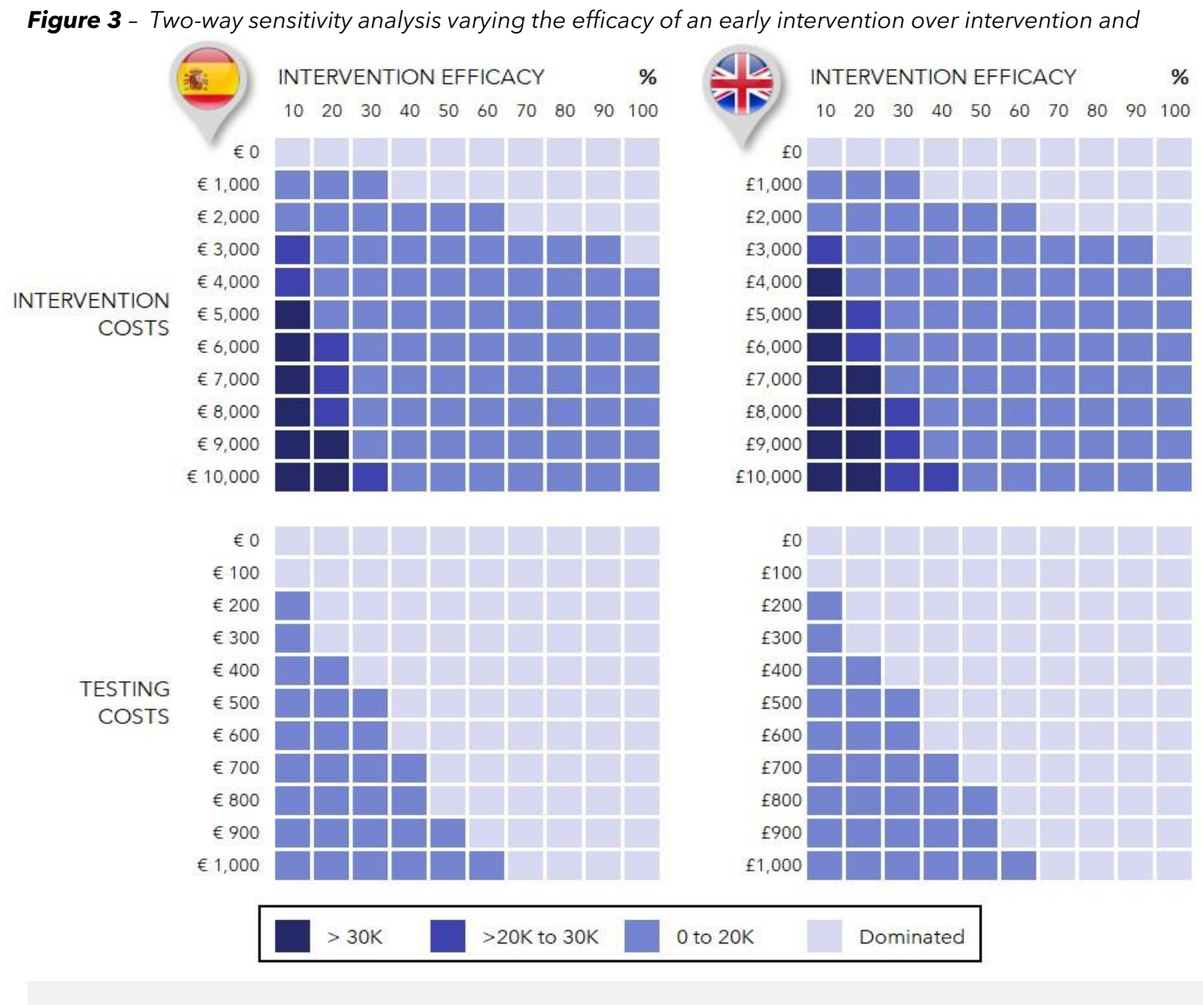
Figure 2 *– Most influential inputs identified in one-way sensitivity analyses*



Acronyms: *ICU, intensive care unit; LOS, length-of-stay; NPS-AKI, non-persistent acute kidney injury; PS-AKI, persistent severe acute kidney injury; QALY, quality-adjusted life year.*

- The TWSA showed that for a 10% efficacy of an early intervention, intervention costs below €5,000 or £3,000 were likely to be cost-effective in Spain and the UK, respectively.
- Testing costs alone were unlikely to affect the cost effectiveness of CCL14 use.
- PSA results were identical to the deterministic for the base case and scenario analyses. In the presence of a minimally effective intervention, CCL14-led care was associated with a 100% probability of being cost-effective at a €30,000/QALY and £20,000/QALY thresholds.

Figure 3 *– Two-way sensitivity analysis varying the efficacy of an early intervention over intervention and*



Discussion

Strengths

- The modelling approach is aligned with published evaluations of AKI biomarkers and has been validated by clinical experts.
- Clinical consequences of PS-AKI were sourced from the analysis of a large dataset, reporting outcomes from over 30,000 people with PS-AKI.
- Uncertainty has been thoroughly investigated in scenario and sensitivity analyses.
- This early exploration analysis investigated the added value of the CCL14 biomarker on predicting PS-AKI in hospitalized individuals with stage 2-3 AKI.

Limitations:

- In the absence of local data specific to PS-AKI, a US publication was used to inform the clinical and cost consequences of PS-AKI.
- Simplified 3-stage Markov model was preferred in the absence of PS-AKI progression to chronic kidney disease.
- As there is no evidence of an intervention preventing PS-AKI, biomarker cost-effectiveness was explored conditionally to a wide range of hypothetical therapeutic effects.
- Cost and adverse events of a hypothetical intervention were assumed not to differ between comparators as it would only be delivered early in the biomarker arm.
- Thirty-day dialysis requirements were used as proxy for lifetime dialysis dependence.

Conclusions

- Further research is required to identify interventions that could prevent PS-AKI after early signalling with CCL14, a biomarker of kidney damage.
- In presence of such a prognostic intervention, identifying individuals at high risk of PS-AKI with CCL14 is likely to be cost-effective in guiding hospital clinical practice in Spain and the UK.

Table 1 *– Incremental results for the base case and scenario analyses*

		CCL14 + SOC		SOC		Incremental		
		Costs	QALYs	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Spain	*Base case*	*€12,203*	*9.893*	*€ 12,366*	*9.818*	*-€ 163*	*0.075*	*Dominated*
	CCL14 cut-off 13 ng/ml	€ 12,303	9.847	€ 12,366	9.818	-€ 63	0.029	Dominated
	Intervention €1,000, test €400	€ 13,186	9.893	€ 12,366	9.818	€ 820	0.075	€ 10,957
	ICU admissions halved	€ 12,399	9.893	€ 12,562	9.818	-€ 163	0.075	Dominated
	30% readmitted to ICU	€ 12,321	9.893	€ 12,483	9.818	-€ 163	0.075	Dominated
UK	*Base case*	*£13,829*	*8.036*	*£13,987*	*7.977*	*-£158*	*0.059*	*Dominated*
	Threshold 13 ng/ml	£13,926	8.000	£13,987	7.977	-£61	0.023	Dominated
	Intervention £1000, test £400	£14,812	8.036	£13,987	7.977	£825	0.059	£14,053
	ICU admissions halved	£13,069	8.523	£13,214	8.472	-£146	0.051	Dominated
	30% readmitted to ICU	£14,128	8.036	£14,285	7.977	-£157	0.059	Dominated

Acronyms: *CCL14, urinary C-C motif chemokine ligand 14 biomarker; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; QALY, quality-adjusted life year; SOC, standard of care.*

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Disclaimer

- This study was sponsored by Baxter International.
- RM, LS, JMP & JM has received consulting fees from Baxter international. EJ & SJ are full-time employees of Baxter International.

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International Society for Pharmacoeconomics and Outcomes Research Europe, 12-15 November 2023, Copenhagen