MSR213

Comparative Efficacy of Treatments in Advanced/ Metastatic Pancreatic Cancer: Demonstrating the Power of Multilevel Network Meta-Regression

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BACKGROUND

- Pancreatic cancer (PC) is the 10th most common cancer in the UK, accounting for around 3% of cancer cases in the UK. PC is associated with a particularly poor prognosis. Between 2017-2019 there were 9,558 deaths from 10,786 cases[1].
- Several network meta-analyses (NMAs) have been performed evaluating treatments for PC, but no publications were found to have used multilevel network meta-regression (ML-NMR).
- While recognized for its benefits in population-adjustment, the ML-NMR framework also offers benefits for performing survival-based NMAs when combining individual patient data (IPD) and aggregate level data (AgD) by integrating the IPD-level likelihood over the AgD-level covariate distributions. At least one covariate is required to "link" the two levels.
- Another key benefit of using the ML-NMR approach is that it allows the proportional hazards (PH) assumption to be relaxed relatively easily. The PH assumption is often violated in PC trials due to the aggressive nature of the disease.
- This poster presents an example of a survival NMA using the ML-NMR framework. This analysis was done to support an MSc dissertation.

OBJECTIVES

- Evaluate the relative efficacy, in terms of overall survival (OS), of treatments for advanced/ metastatic PC using the ML-NMR framework to conduct a non-PH survival NMA.
- Corroborate findings of previous NMAs of treatments for patients with PC, which suggested FOLFIRINOX (FOL), gemcitabine plus nab-Paclitaxel (GEM-NAB), and gemcitabine plus capecitabine (GEM-CAP) give superior OS benefit compared to GEM monotherapy.
- Provide clarity on the comparison between GEM-NAB and GEM-CAP for the treatment of PC, which has been noted as "uncertain" in current NICE guidance for the treatment of PC[2].

METHODS

1. OS Kaplan-Meier (KM) curves from eight studies were digitized, and survival-data reconstructed using the Guyot algorithm[3]. Studies were identified through desktop research (Google Scholar and PubMed) targeted to identify phase III trials of locally advanced/metastatic non-resectable PC (due to most PC cases being non-resectable)[4]. Studies were excluded if they included a surgery arm and were required to present OS curves with numbers at risk for digitizing. Figure 1 demonstrates the network of evidence generated by the studies.

2. Parametric survival models were fitted to each treatment arm within each study. The three best models (determined by Akaike information criterion [AIC] scores and visual inspection of fit to KM curves) were used as likelihoods in the ML-NMR. Only three survival models were used due to the long run-time of ML-NMR models.

3. The ML-NMR was performed using the multinma R package[5]. Both fixed effect (FE) and random effects (RE) models were fit using 1000 (500 warmup, 500 sampling) iterations on four chains. FE models were deemed appropriate due to the extent of homogeneity in the trial populations in terms of cancer type, age, and sex. In the absence of access to IPD from any of the identified studies, data had to be simulated for one of the studies. This was done using the proportion of male patients from one of the studies to randomly assign patients to either male or female. By having at least one covariate, the ML-NMR method could be used. Sex was the only variable that could be simulated without introducing any assumptions about covariate distributions.

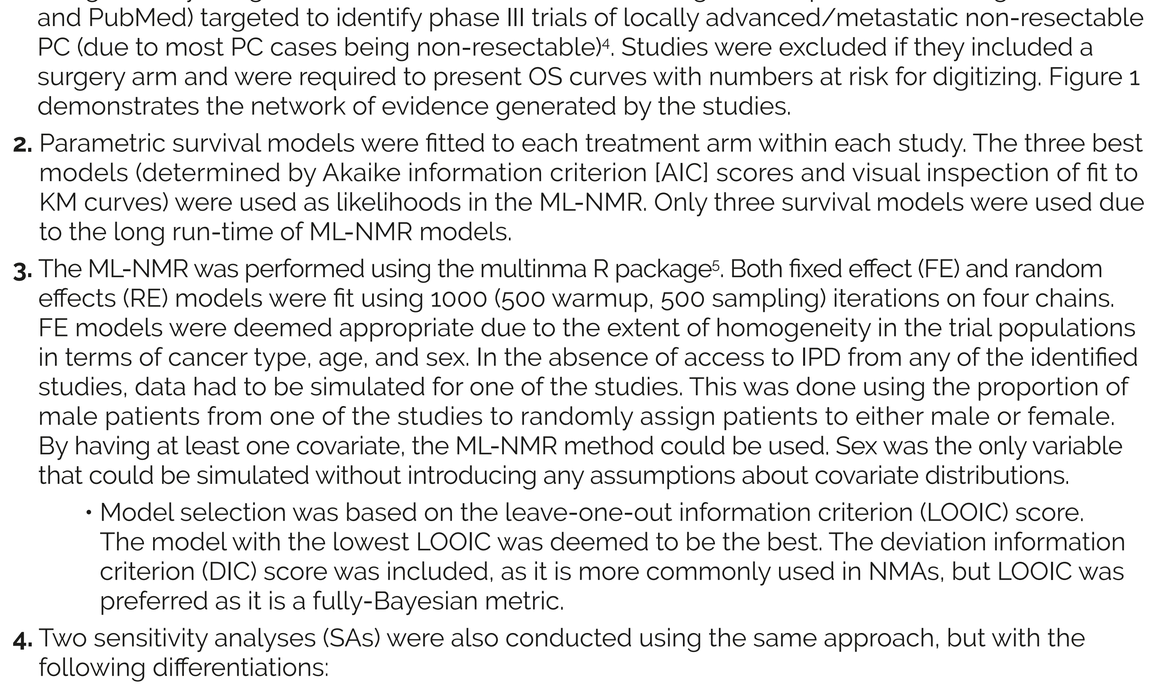
- Model selection was based on the leave-one-out information criterion (LOOIC) score. The model with the lowest LOOIC was deemed to be the best. The deviation information criterion (DIC) score was included, as it is more commonly used in NMAs, but LOOIC was preferred as it is a fully-Bayesian metric.

4. Two sensitivity analyses (SAs) were also conducted using the same approach, but with the following differentiations:

a) Removal of any trials with immature KM data (defined as trials not achieving OS < 0.20) to assess the effect of data maturity on model convergence.

b) Removal of FOL from the network of evidence, as it can only be given to patients who are fit enough to tolerate the increased toxicity.

Figure 1. Base case network of evidence



Abbreviations: AgD: aggregate data; AXI: axitinib; CAP: capecitabine; IPD: individual patient data; IRI: irinotecan; NAB: nab-paclitaxel; PEM: pemetrexed; SOR: sorafenib; FOL: FOLFIRINOX.

Note: The study of GEM-NAB versus GEM was chosen to simulate IPD given its very mature data and relatively large sample size. Further, it was included in the base case and both SAs.

RESULTS

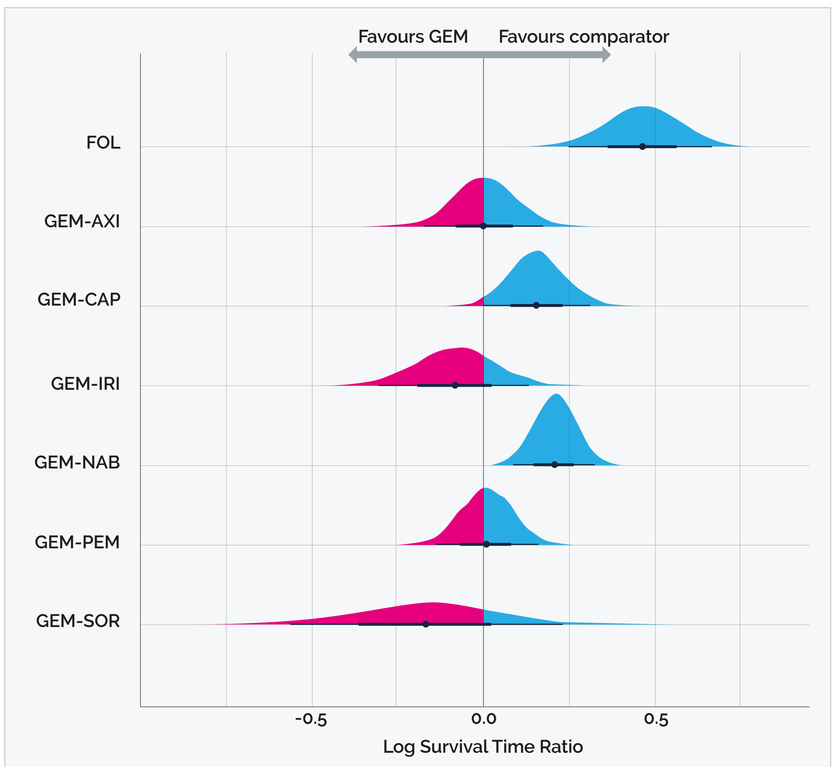
- The gamma, generalized gamma, Gompertz, log-logistic, log-normal, and Weibull models were fit to the KM curves. Of these, the log-logistic, log-normal, and Weibull models were the three best fitting, based on AIC and visual inspection, and were therefore used in the ML-NMR. The fit statistics of these three models is presented in Table 1.
- While the log-logistic RE model scored best in terms of the LOOIC scores, the log-logistic FE model scored very close to the RE model. The convergence of both models was therefore considered by examining the trace plots and pairwise-coordinate plots. The FE log-logistic model demonstrated better convergence than the RE model and was therefore selected.

Table 1: Model selection statistics for each model

LIKELIHOOD	FIXED EFFECT		RANDOM EFFECTS	
	DIC	LOOIC	DIC	LOOIC
LOG-LOGISTIC	16974	16974	**16972**	**16973**
LOG-NORMAL	107813405	48652	16978	16974
WEIBULL	16989	16993	3.194×10^{42}	5.846×10^{21}

Abbreviations: DIC: deviation information criterion; LOOIC: leave-one-out information criterion.

Figure 2: Pairwise comparisons (log survival time ratio) of comparators with GEM



Abbreviations: AXI: axitinib; CAP: capecitabine; IRI: irinotecan; NAB: nab-paclitaxel; PEM: pemetrexed; SOR: sorafenib; FOL: FOLFIRINOX.
Note the bold black line around the point estimates represents the 95% credible interval, and the thinner line is the 80% credible interval.

- Figure 2 presents the base-case results from the ML-NMR using the FE log-logistic model survival model. The results are presented in terms of the log survival time ratio (the natural log of the ratio of restricted-mean survival time [RMST] values for the comparator and GEM) compared with GEM.
- FOL and GEM-NAB both gave significant OS benefits compared to GEM whereas GEM-AXI and GEM-PEM provided no significant benefit compared to GEM. GEM-IRI and GEM-SOR provided worse OS compared with GEM and other comparators. GEM-SOR was noted for having a wide credible interval due to low patient numbers.
- In the first SA, GEM-NAB and GEM-CAP again gave superior OS compared to GEM, but the difference was not significant, as in the base case.
- The results of the SAs showed that the RE models had better convergence with more mature data and that, where FOL is not an option, GEM-NAB should be considered first.

CONCLUSIONS AND RECOMMENDATIONS

1. Compared with GEM, FOL provided the most favorable OS improvement, followed by GEM-NAB and GEM-CAP. FOL was the only other treatment to significantly improve OS compared to GEM.

2. This dissertation acted as a proof-of-concept for the use of ML-NMR for assessing treatments for advanced/metastatic PC. By using this method on IPD with more covariates, it would be possible to understand treatments for this disease at a more granular level.

3. While the results were in line with previous NMAs[6,7] in terms of FOL, GEM-NAB, and GEM-CAP providing the most OS benefit compared to GEM, it would be wise to perform this method on data from a full systematic literature review (SLR) to obtain a wider overview of the therapy options for PC. Due to time-limitations of the dissertation, an SLR could not be performed for this project.

4. In the second SA, the RE models had better convergence, suggesting that the RE ML-NMR models are more sensitive to data maturity than the FE models. Further research could be done in this area to determine how sensitive the ML-NMR method is to data maturity.

REFERENCES

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M. Knowles performed the study described in this poster as part of his MSc dissertation, supervised by **Dr. S. Ren**. You can read the full dissertation using the QR code.

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