

Pharmacometric Time-to-Event (TTE) Modeling of Diabetic Nephropathy in Type 2 Diabetes Mellitus Patients

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Background and Purpose

Time-to-event (TTE) pharmacometric analysis has an important role in the parametric quantification of the occurrence of diabetic nephropathy. Incorporating censoring event and time components in the TTE analysis allow unbiased and better estimates of survival function than the traditional regression methods. The present study focused on the development of TTE model of diabetic nephropathy among patients with type 2 diabetes mellitus (T2DM).

Methods

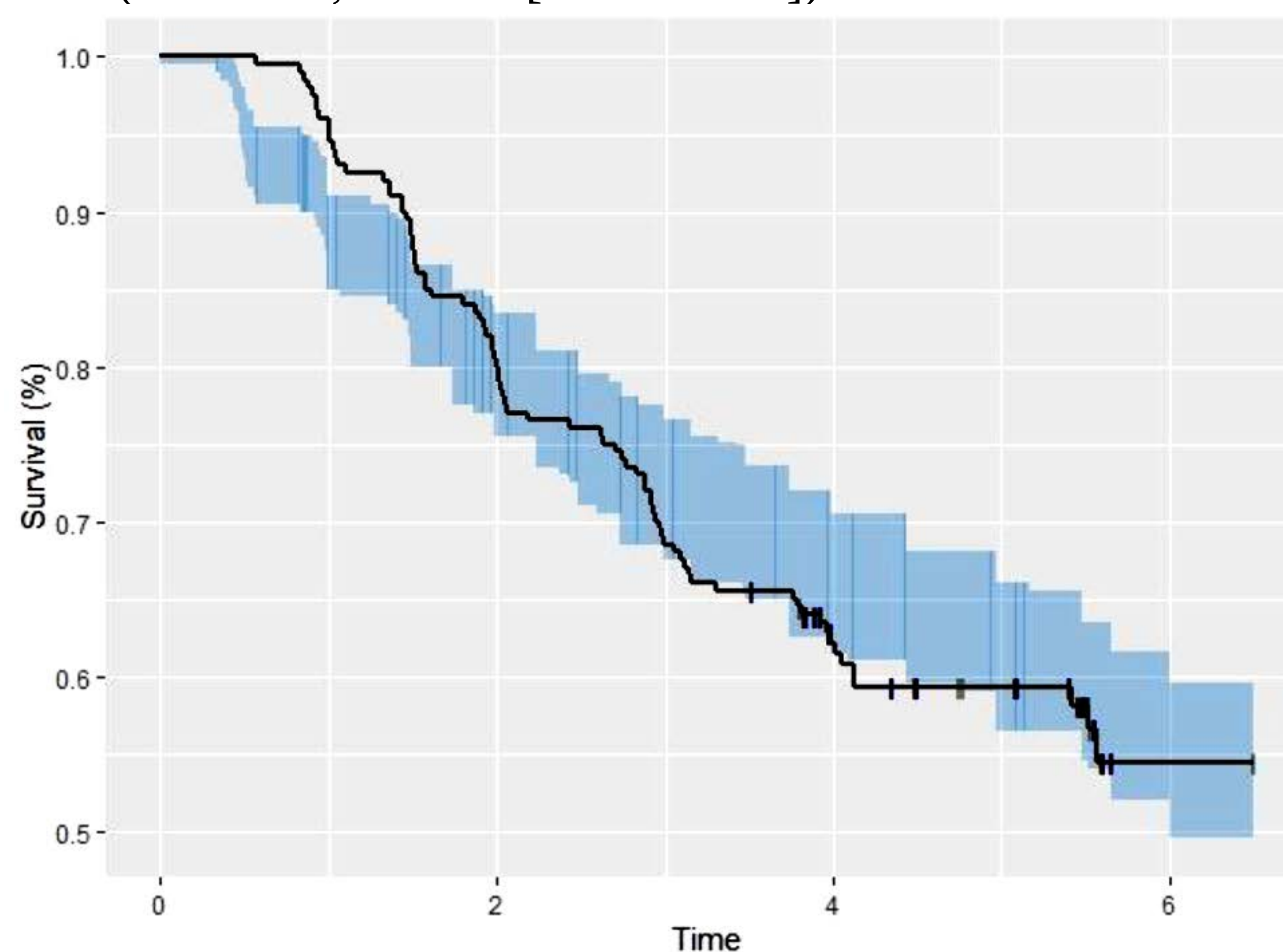
The data was collected from a tertiary care hospital comprising of 200 T2DM patients. The maximum follow up period was about 6.5 years. Parametric TTE analysis was performed using NONMEM software. The event was defined by the development of diabetic nephropathy (persistent proteinuria for three visits). Three TTE models; exponential, Gompertz and Weibull hazard models were tested for base model. The effect of covariates on the overall hazard of developing diabetic nephropathy was investigated using stepwise approach. The likelihood ratio test (LRT) with a significance level (α) of 5% was used to discriminate between nested models. The selection of final model was based on the lowest OFV, Kaplan Meier visual predictive check (KM-VPC) with 100 simulations, relative standard error (RSE) as well as the scientific plausibility.

Results

Out of 200 patients, 82 (41%) patients developed diabetic nephropathy. The best base model was exponential hazard model with the baseline hazard of 1.5068 /year (RSE=31%). The hazard of developing diabetic nephropathy decreases with the use of angiotensin receptor blockers (ARBs) (HR, 0.454; 95% CI [0.628-0.328], with 1-year increment in age (HR, 0.965; 95% CI [0.980-0.950] as well as having the eGFR of > 90ml/min (HR, 0.278; 95% CI [0.580-0.118]. Having eGFR of 60-89 ml/min and <60 ml/min increase the risk of diabetic nephropathy with HR 2.44; 95% CI [1.783-3.338] and HR 4.392; 95% CI [3.101-6.222], respectively. The summary of parameters can be found in Table 1.

Parameter	Description	Typical Value	Relative estimation error (RSE%)
λ_0	Baseline hazard at time of enrolment	0.41	31
$\theta_{\text{EGFR}=1}$	Effects of EGFR=1 on hazard	-1.28(0.278)	34
$\theta_{\text{EGFR}=2}$	Effects of EGFR=2 on hazard	0.892(2.44)	18
$\theta_{\text{EGFR}=3}$	Effects of EGFR=3 on hazard	1.48(4.393)	12
θ_{ARBs}	Effects of ARBs on hazard	-0.789(0.454)	21
θ_{AGE}	Effects of AGE on hazard	-0.0354(0.965)	22

- The best base model was exponential hazard model with the baseline hazard of 1.5068 /year (RSE=31%).
- Angiotensin receptor blockers (ARBs) decreases the risks of development of DN(HR, 0.454; 95% CI [0.628-0.328]).
- With 1-year increment in age, the risk of DN decreases (HR, 0.965; 95% CI [0.980-0.950]).
- eGFR of > 90ml/min reduce the risks of development of DN (HR, 0.278; 95% CI [0.580-0.118]).
- eGFR of 60-89 ml/min increase the risk of diabetic nephropathy (HR 2.44; 95% CI [1.783-3.338]).
- eGFR <60 ml/min increase the risk of diabetic nephropathy (HR 4.392; 95% CI [3.101-6.222])



- Black line: observed median data
- Grey area: 95% prediction interval
- 100 samples

Conclusions

These approaches may not only improve the medical practitioners understanding about disease progression but will also be helpful in improving treatment strategies. Present study found that ARBs can be helpful in minimizing the risk of developing diabetic nephropathy while eGFR trend can be useful indicator for diabetic nephropathy.

References

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