

FEATURED ARTICLE

A prognostic model for overall survival in sporadic Creutzfeldt-Jakob disease

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Abstract

Introduction: We developed a prognostic model for overall survival after diagnosis of sporadic Creutzfeldt-Jakob disease (sCJD) using data from a German surveillance study.**Methods:** We included 1226 sCJD cases (median age 66 years, range 19–89 years; 56.8% women with information on age, sex, codon 129 genotype, 14-3-3 in the cerebrospinal fluid (CSF), and CSF tau concentrations. The prognostic accuracy for overall survival was measured by the c statistics of multivariable Cox proportional hazard models. A score chart was derived to predict 6-month survival and median survival time.**Results:** A model containing age, sex, codon 129 genotype, and CSF tau (with two-way interactions) was selected as the model with the highest c statistic (0.686, 95% confidence interval: 0.665–0.707) in a cross-validation approach.**Discussion:** We developed the first prognostic model for overall survival of sCJD patients based on readily available information only. The developed score chart serves as a hands-on prediction tool for clinical practice.

KEYWORDS

biomarker, cerebrospinal fluid, neurodegeneration, prognosis, sporadic Creutzfeldt-Jakob disease, tau

1 | BACKGROUND

Prion diseases (or transmissible spongiform encephalopathies) are invariably fatal rapidly progressive neurodegenerative diseases caused by the misfolding of the cellular prion protein (PrP_c) into an abnormal pathological disease-associated form prion protein scrapie (PrP^{Sc}) that propagates and aggregates in the brain tissue, leading to massive neuronal damage and spongiform degeneration. Among human prion

diseases, sporadic Creutzfeldt-Jakob disease (sCJD) accounts for 85% to 90% of all cases with an incidence rate of 1 to 2 cases per million per year.^{1,2}

The diagnosis of sCJD is based on progressive dementia plus at least two further clinical symptoms. Neuroimaging, typical electroencephalogram (EEG) pattern, and cerebrospinal fluid (CSF) biomarkers are supportive tools included in the diagnostic criteria of sCJD.³ A confirmatory diagnosis of sCJD requires neuropathological assessment of

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brain tissue obtained either at biopsy or at autopsy. The combination of neuropathological information on PrPSc type (one or two based on the size of protease-resistant fragments) and genotype at codon 129 in the *PRNP* gene (methionine or valine) gives rise to different sCJD subtypes with characteristic disease phenotypes and neuropathological features.⁴

While diagnostic criteria for sCJD show a high accuracy, there are no prognostic models that could be used to predict disease progression after onset of disease. Heterogeneity is observed regarding disease duration, which averages 5 to 6 months, but ranges from weeks to several years.^{1,5} Identification of determinants influencing disease severity and disease duration may shed light on the pathophysiological mechanisms of the disease and turn into valuable tools for selection and stratification of patients for potential clinical trials and evaluation of therapeutic interventions. Moreover, estimated survival times are essential pieces of information crucial for families and caretakers to plan further health care and to maximize the patient's quality of life. In previous studies, more prolonged survival was associated with younger age at onset, sex, codon 129 genotype, and PrPSc type.^{5,6} The role of CSF biomarkers as a potential source of biochemical predictors of survival time was not investigated until recent years.

CSF tau,⁷⁻⁹ α -synuclein,¹⁰ neurofilament light,¹¹ and neurogranin,¹² as well as plasma tau,⁷ have been recently proposed to be associated with survival time. Based on a cohort study including 188 participants, Staffaroni et al.⁷ concluded that CSF tau levels (among other fluid biomarkers) could be used to predict survival of sCJD patients; however, in their study Staffaroni et al. only reported hazard ratios, that is, measures of relative effect, which are not suitable for evaluating the prognostic potential of predictive models. To predict an individual's survival probability, absolute risks are needed as a basis for calculating measures of prognostic accuracy.¹³ In the present study, we aimed to develop and assess the performance of an individual prognostic prediction model based on CSF biomarkers and other proposed disease survival modifiers easily obtainable in a routine setting at time of diagnosis. We used a large surveillance-based cohort study, which allowed cross-validation of estimates of prognostic accuracy.

2 | METHODS

2.1 | Selection and description of participants

Case data were collected in the framework of a surveillance-based prospective cohort study conducted by the German Reference Centre for Transmissible Spongiform Encephalopathies (NRZ-TSE) at the University Medical Center Göttingen.¹ In Germany, suspected sCJD is subject to notification and treating institutions are instructed to consult the NRZ-TSE. Between 1993 and 2017, a 2908 patients were diagnosed with probable or definite sCJD in Germany according to the criteria by Zerr et al.³ for probable cases (clinical definition) and by Parchi et al.¹⁴ for definite cases (neuropathological confirmation). Referring physicians or physicians of the CJD surveillance unit were advised to ask the next of kin of the patient to determine the time

HIGHLIGHTS

- Development of individual prognostic model using data from large cohort study on sporadic Creutzfeldt-Jakob disease.
- Model with age, sex, genotype, cerebrospinal fluid tau (with two-way interactions) had good accuracy.
- New score chart serves as a hands-on prediction tool for clinical practice.

RESEARCH IN CONTEXT

1. **Systematic review:** Sporadic Creutzfeldt-Jakob disease is the world's most common invariably fatal human prion disease (incidence rate: 1 to 2 cases per million per year). Disease duration averages 5 to 6 months from diagnosis to death, but ranges from weeks to several years. Currently no prognostic models can predict median disease duration.
2. **Interpretation:** We developed an individual prognostic model with moderate to good accuracy for predicting overall survival based on routinely available information at the time of diagnosis (demographic factors, codon 129 *PRNP* genotype, and cerebrospinal fluid tau levels).
3. **Future directions:** The moderate accuracy provides room for improvement of the model, by including additional parameters (based on imaging, symptoms, or biomarkers), which might currently not be available at all clinical centers. We derived a score chart that allows easy prediction of 6-month survival and median disease duration, and is suitable for tests on clinical grounds for its usefulness.

of onset within a range of 2 weeks (beginning, middle, or end of the month). Occurrence of any cognitive disturbance or progressive behavioral change indicating onset of dementia as well as first impression of any form of progressive movement disturbance were defined as sCJD onset. All patients were followed up until death, and dates, as well as causes of death, were validated using official death certificates. From the 2908 patients diagnosed with sCJD in the study period, 1386 (48%) had no information on codon 129 genotype, 72 (2%) had no lumbar puncture taken, 85 (3%) had no information on the date of death, and for 139 (5%) no tau values were available, so a total of 1226 individuals could be included in the study. Lumbar punctures were performed at time of first routine diagnostic workup. The present study was conducted according to the revised Declaration of Helsinki and Good Clinical Practice guidelines and has been approved by the local ethics committee in Göttingen (No. 11/11/93). All patients or their next of kin gave written informed consent.

2.2 | Technical information

CSF total-Tau (tau) was quantified using the INNOTEST hTAU Ag enzyme-linked immunosorbent assay (ELISA) kit from Fujirebio-Europe (Ghent, Belgium). All CSF tau measurements were performed in the same institution (Neurochemistry Laboratories of the Department of Neurology, University Medical Center Göttingen), which performs internal quality controls and participates regularly in ring trials. During the period of the study, the assay used and its cut-offs were not changed. In addition, longitudinal drifts of CSF tau levels were not detected. The presence of 14-3-3 protein was analyzed by western blot as described previously.¹⁵ Inconclusive 14-3-3 tests were reported as negative. For the assessment of codon 129 genotype in the prion protein gene (*PRNP*), genetic testing was performed as described before.¹⁶ sCJD subtype was determined following established neuropathological criteria.¹⁴

2.3 | Statistical analysis

All analyses were performed with R version 3.6.1 (www.R-project.org). We did a complete case analysis, which is preferable to multiple imputations when only the outcome variable has missing values¹⁷ (as in this case, standard errors from multiple imputations are likely to be larger than those of complete case analysis). Tau levels among genotypes were compared using analysis of variance (ANOVA). Based on expert knowledge, age, sex, 14-3-3 positivity, genotype, and CSF tau were chosen as candidate predictors for a prognostic model with disease duration (time from first reported symptom to death) as outcome. CSF tau levels were log-transformed using the natural log to fulfil the normal distribution assumption. Nine different Cox proportional hazard models were derived: a model containing only age and sex; three models containing age, sex, and one additional candidate predictor; three models containing age, sex, and two additional candidate predictors; and a model containing all five candidate predictors. Potential two-way interactions between predictors were investigated by likelihood-ratio tests. A penalized spline (R package "survival"¹⁸ version 2.44-1.1) for tau was considered, but results did not differ from the results obtained when using log-transformed tau. For each model, predicted 6-month survival probabilities (R package "pec"¹⁹ version 2018.07.26) were estimated with 10-fold cross-validation. Concordance (c) statistics¹³ based on the predicted 6-month survival probabilities were calculated for each model. Jack-knife estimation²⁰ was used to assess c statistic improvement when adding a candidate predictor to a model (R package "validstats"²¹ version 1.4). Adjustment for multiple testing was performed by applying the false discovery rate.²² The model with the highest c statistic was chosen for further analyses.

Calibration was performed using 10-fold cross-validated Kaplan-Meier estimates obtained by stratifying patients by the predicted probability, with at least 100 patients per group (R package "rms"²³ version 5.1-3.1). A score chart^{24,25} was derived as a hands-on tool to easily predict 6-month survival and median survival time in clinical

practice. Points were assigned to values of age (20 to 90 years in 5-year steps), sex, genotype, and tau (with cut points 250; 500; 1000; 2500; 5000; 10,000; 25,000; 50,000 pg/mL) based on the Cox regression coefficients. The points measure the contribution of the values of the predictor variables on the "linear predictor" scale.²⁶ For each possible sum of points, the survival probability can be derived from $S(t) = S_0(t)^{\exp(\text{total points})}$ where $S(t)$ denotes the survival function and $S_0(t)$ denotes the baseline survival function for an individual whose covariates are equal to zero.²⁷ Confidence intervals for the survival probability were derived from the standard errors of the regression coefficients. The median survival time is the time by which half of the patients with a defined sum of points have died. To investigate the deviation of the observed from the predicted survival probability, the proportion of patients with a disease duration of 6 months or more (ie, the observed 6-month survival probability) was calculated among patients stratified by the predicted 6-month survival probability. For this, patients were assigned (a) the point estimate, (b) the lower, or (c) the upper limit of the 95% confidence interval (CI) of the predicted 6-month survival probability.

To investigate if results were consistent among different levels of certainty of sCJD diagnosis, sensitivity analyses were performed (1) among definite sCJD cases only, (2) among probable sCJD cases only, and (3) among patients with known molecular subtype. In each of these three subgroups, the following steps were conducted in line with the primary analysis. Nine different Cox proportional hazard models were derived, each including a combination of the variables age, sex, 14-3-3 positivity, genotype (or molecular subtype in the third sensitivity analysis), and CSF tau. C statistics based on the predicted 6-month survival probabilities were calculated for each model. Jack-knife estimation was used to assess c statistic improvement when adding a candidate predictor to a model.

3 | RESULTS

3.1 | Patients

Among the 1226 sCJD cases, there were 655 definite and 571 probable cases. Forty-three percent of the patients were male (Table 1). The median age at diagnosis was 66 years (interquartile range 60–73 years, range 19–89 years); the majority of patients had a positive 14-3-3 test result (86.0%). Among these patients, tau levels differed between genotypes, irrespective of the level of certainty of sCJD diagnosis (Figure 1). Among patients with a negative 14-3-3 test result, there was no evidence for differences in tau levels between genotypes. All patients died during follow-up; the median disease duration was 6 months (interquartile range 3.5–11 months, range 1–47 months). sCJD was registered as the underlying cause of death in the death certificates of all included cases according to World Health Organization cause of death definitions. Clinically, this translated into a rapidly progressive neuropsychiatric syndrome leading to akinetic mutism.

TABLE 1 Baseline characteristics by level of certainty of sCJD diagnosis

	All sCJD cases (n = 1,226)	Definite sCJD cases (n = 655)	Probable sCJD cases (n = 571)
Age (years)	66.0 (60.0, 73.0)	66.0 (59.0, 73.0)	66.0 (61.0, 73.0)
Sex			
Female	696 (56.8)	377 (57.6)	319 (55.9)
Male	530 (43.2)	278 (42.4)	252 (44.1)
14-3-3 positivity	1054 (86.0)	582 (88.9)	472 (82.7)
Codon 129 genotype			
MM	775 (63.2)	451 (68.9)	324 (56.7)
MV	234 (19.1)	99 (15.1)	135 (23.6)
VV	217 (17.7)	105 (16.0)	112 (19.6)
Molecular subtype			
MM1	202 (16.5)	190 (29.0)	12 (2.1)
MM1/2	6 (0.5)	5 (0.8)	1 (0.2)
MM2	15 (1.2)	14 (2.1)	1 (0.2)
MV1	37 (3.0)	34 (5.2)	3 (0.5)
MV2	23 (1.9)	21 (3.2)	2 (0.4)
VV1	10 (0.8)	10 (1.5)	0 (0)
VV2	48 (3.9)	46 (7.0)	2 (0.4)
Unknown subtype	885 (72.2)	335 (51.1)	550 (96.3)
Tau (pg/mL)	5198.5 (2521.9, 10535.8)	5404.0 (2753.7, 11542.5)	4764.0 (2088.0, 9633.7)
log(tau) (log(pg/mL))	8.6 (7.8, 9.3)	8.6 (7.9, 9.4)	8.5 (7.6, 9.2)
Disease duration (months)	6.0 (3.5, 11.0)	5.0 (3.0, 10.0)	6.5 (3.5, 12.0)
Death within 6 months after sCJD diagnosis	647 (52.8)	374 (57.1)	273 (47.8)

Note: Data are medians (25th percentile, 75th percentile) or numbers (percentage).

Abbreviation: sCJD, sporadic Creutzfeldt-Jakob disease.

3.2 | Prognostic prediction model

All candidate predictors were associated with disease duration in the unadjusted analyses (Table 2). The Cox proportional hazards model containing age and sex had a c statistic of 0.597 (95% CI 0.574–0.620; Figure 2), representing a moderate ability to predict survival at 6 months. Adding any of the other three variables to this model significantly improved the c statistic (Figure 2). Adding another variable to these three-variable models further improved the c statistic by a small margin. The model containing age, sex, and all three variables had a higher c statistic than the models containing age, sex, 14-3-3 positivity, and either genotype or tau. However, adding 14-3-3 positivity to the model containing age, sex, genotype, and tau neither improved the c statistic (Figure 2) nor changed the hazard ratios of the other candidate predictors (Table 2). Thus, we chose the model containing age, sex, genotype, and tau as the final model for further analyses. The two-way interaction terms age \times tau, sex \times tau, and sex \times genotype significantly increased the model fit (likelihood-ratio test $P = 0.008$, $P = 0.03$, and $P = 0.008$, respectively). Although the c statistic did not increase by including these interaction

terms (0.686, 95% CI 0.665–0.707), these three interaction terms were kept in the model during subsequent analyses. Including an interaction term between genotype and tau did not improve the model (likelihood-ratio test $P = 0.65$); neither did using a non-linear effect for tau.

The selected prognostic model was calibrated well (Figure A.1 in supporting information) and the observed median disease duration was well captured by the predicted median disease duration (Figure A.2 in supporting information). The baseline survival (information that is necessary for calculating individual risk²⁸) was 99.6% at 1 month. A score chart was derived to predict 6-month survival and median disease duration based on the selected model (Figure 3). According to this score chart, a 65-year-old woman with genotype MM and a tau level of 1000 pg/mL receives 62 points, which correspond to an estimated median survival time of 9 months. The confidence intervals of the predicted 6-month survival are shown in Figure A.3 and Figure A.4 in supporting information. When patients are stratified by the predicted 6-month survival probability, the proportion of patients with a disease duration of 6 months or more (ie, the observed 6-month survival probability) is represented well by the

TABLE 2 Cox proportional hazard models with disease duration as the outcome

	Unadjusted HR for each candidate predictor		Model including all candidate predictors		Final prediction model			
	All sCJD cases (n = 1,226)		All sCJD cases (n = 1,226)		All sCJD cases (n = 1,226)		Definite sCJD cases (n = 655)	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Main effects								
Age (per 5 years)	1.13 (1.09–1.17)	<.001	1.13 (1.09–1.17)	<.001	1.59 (1.22–2.07)	<.001	1.68 (1.17–2.42)	.005
Male vs female	1.21 (1.08–1.36)	<.001	1.51 (1.34–1.70)	<.001	0.96 (0.34–2.67)	.93	1.47 (0.35–6.20)	.60
14-3-3 positivity	1.92 (1.63–2.26)	<.001	1.10 (0.91–1.34)	.31	NA	NA	NA	NA
Codon 129 genotype								
MM	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
MV	0.49 (0.43–0.57)	<.001	0.59 (0.51–0.70)	<.001	0.70 (0.56–0.86)	.001	0.80 (0.58–1.12)	.20
VV	0.91 (0.78–1.06)	.22	0.95 (0.81–1.10)	.49	1.07 (0.88–1.30)	.5	0.97 (0.74–1.28)	.83
log(tau) (per unit)	1.46 (1.38–1.55)	<.001	1.35 (1.26–1.45)	<.001	2.28 (1.49–3.48)	<.001	2.54 (1.43–4.51)	.001
Interaction effects								
Age × log(tau)					0.96 (0.93–0.99)	.01	0.95 (0.92–0.99)	.026
Male sex × log(tau)					1.07 (0.95–1.20)	.24	1.01 (0.86–1.19)	.90
Male sex × genotype MV					0.69 (0.50–0.94)	.02	0.68 (0.43–1.07)	.094
Male sex × genotype VV					0.73 (0.54–1.00)	.048	0.87 (0.56, 1.35)	.53

Abbreviations: CI, confidence interval; HR, hazard ratio; sCJD, sporadic Creutzfeldt-Jakob disease.

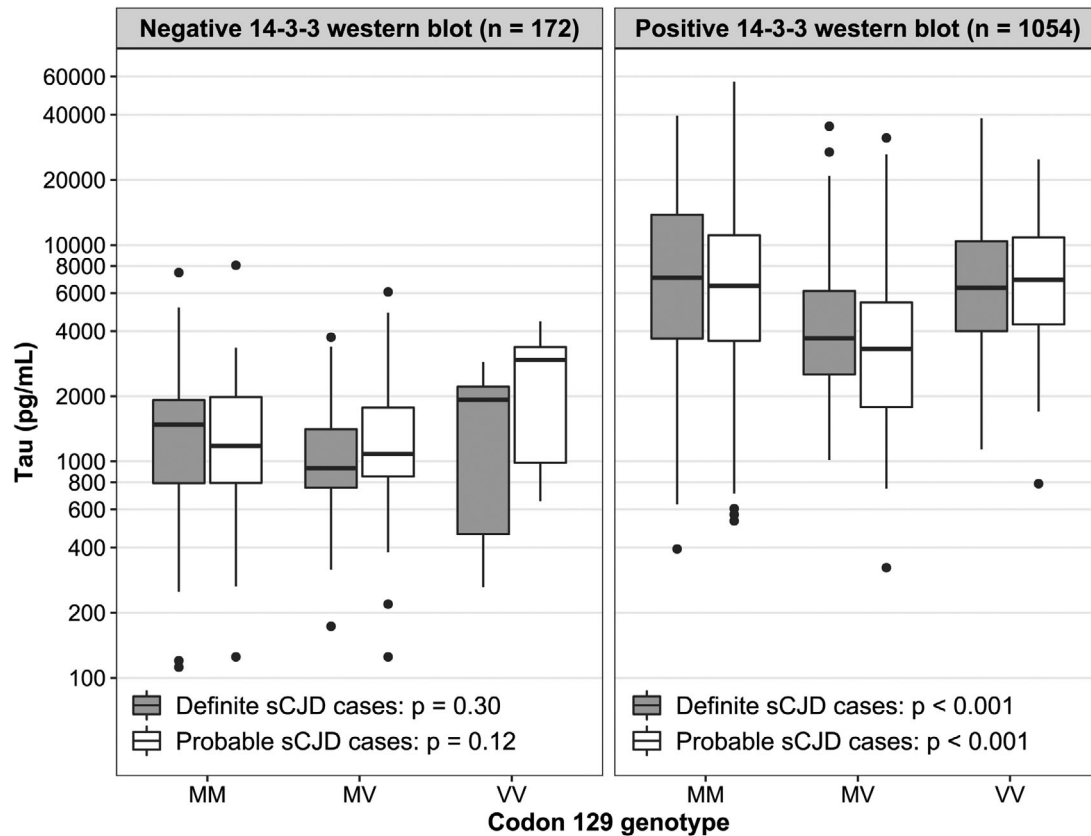


FIGURE 1 Concentrations of tau by the level of certainty of sporadic Creutzfeldt-Jakob disease diagnosis and result of 14-3-3 test. The *P* values refer to Kruskal-Wallis tests of differences in the distribution of tau among the three genotypes

predicted probability and its confidence intervals (Figure A.5 in supporting information).

3.3 | Sensitivity analyses

In the subgroup of definite sCJD cases (*n* = 655; 374 deaths at 6 months), results were similar to the main analysis; the model containing age, sex, genotype, and tau had the highest *c* statistic (Figure A.6 in supporting information). Including the interaction term age × tau improved the model fit but did not increase the *c* statistic (0.667, 95% CI 0.638–0.695).

In the subgroup of probable sCJD cases (*n* = 571; 273 deaths at 6 months), there were two models that met our selection criterion for the final model: the model containing age, sex, genotype, and tau had a nearly equally high *c* statistic as the model containing age, sex, genotype, and 14-3-3 positivity (Figure A.7 in supporting information). Including interaction terms between sex and either genotype, tau, or 14-3-3 positivity improved the model fit but did not increase the *c* statistic (0.703, 95% CI 0.671–0.735).

When using the information on molecular subtype instead of genotype in the subgroup of patients with known molecular subtype, the model containing age, sex, subtype, and tau had the highest *c* statistic (Figure A.8 in supporting information). Including the interaction term

sex × tau improved the model fit but did not increase the *c* statistic (0.682, 95% CI 0.642–0.721).

4 | DISCUSSION

In this study, we developed an individual prognostic model with moderate to good accuracy for predicting overall survival after sCJD diagnosis based on routinely available information at the time of diagnosis (demographic factors, codon 129 *PRNP* genotype, and CSF tau levels). We derived a score chart for this model, which allows easy prediction of 6-month survival and median survival time in clinical practice.

While several previous studies assessed risk factors of survival time in sCJD, none of them translated their results into a prognostic model.^{7–12} Because even large relative effect estimates (and small *P* values) in risk factor analyses do not necessarily result in good prognostic accuracy, our study adds a previously ignored dimension into the discussion on how well survival time in sCJD can be predicted.

All factors included in our model contributed to the overall prognostic accuracy, although individual effects were rather small. The overall accuracy is only on a moderate level, which results in relevant uncertainty about predicted survival times. However, calibration results suggest that predicted survival estimates differ from true survival rates only when true 6-month survival probabilities are high (Figure A.1).

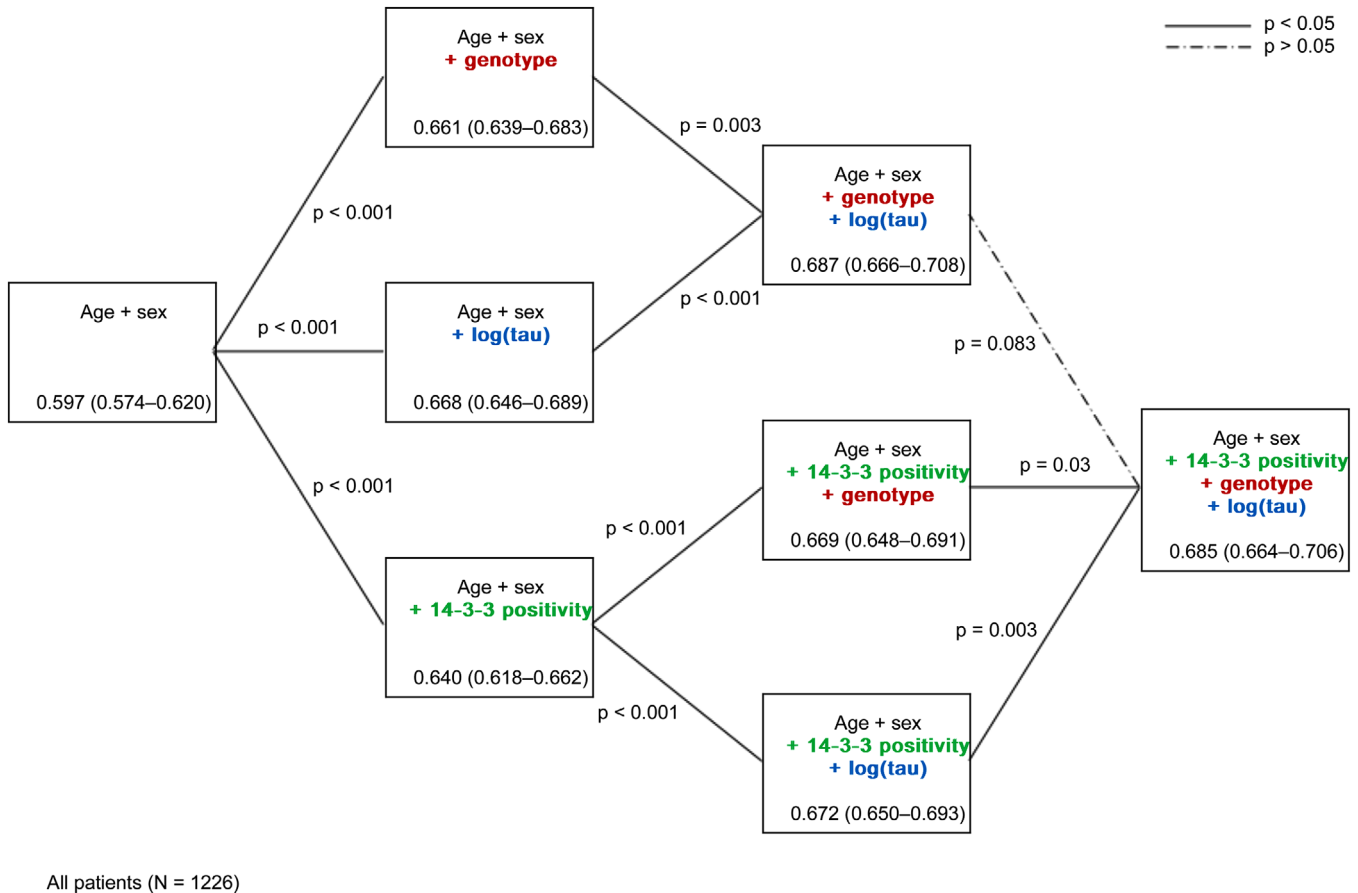


FIGURE 2 c statistics for all Cox regression models and jack-knife estimation for c statistic improvement between models among all sCJD cases (n = 1226). For each model, the c statistic with 95% confidence interval is reported. The model containing age, sex, genotype, and log(tau) was chosen for the final analysis

After taking into account the four factors included in the prognostic model, 14-3-3 measured in CSF did not provide added value in the prognostic model. This is reasonable because 14-3-3 measures the intensity of neuronal damage, which is also represented by tau. Moreover, 14-3-3 was measured as a binary variable only in our study, making it less suitable as a prognostic marker than the quantitatively measured tau.

Because CSF tau is mainly a marker of neuro-axonal damage, it seems plausible that the degree of neuronal damage (which might not be equivalent to the severity of symptoms) at the time of diagnosis is the underlying factor that can predict the progression of the disease. If this holds, then other CSF surrogate markers of neuronal damage may also be useful prognostic markers, similar to tau. Given the high correlation between tau and 14-3-3 positivity in sCJD cases and the recent introduction of quantitative 14-3-3 measurements in clinical set-up,²⁹ it could be interesting to determine the prognostic value of 14-3-3 as a continuous variable either alone or in combination with tau.

Similarly, the present approach opens the possibility to explore the prognostic accuracy of markers associated with other aspects of prion pathogenesis such as synaptic damage, neuro-inflammation, or PrP conversion. Associations between disease duration and CSF biomarkers levels have already been reported for neurogranin (synaptic/axonal

damage marker),¹² α -synuclein (pre-synaptic damage marker),¹⁰ and neurofilament light (white matter damage).¹¹ However, these biomarkers were not available in our study population, and have not been assessed for their prognostic accuracy in the past.

4.1 | Limitations

We were only able to include about half of the patients diagnosed in the study period in this analysis. Almost all of the patients not included did not have information on their codon 129 genotype, which was considered a relevant potential prognostic factor a priori. Decision for or against genetic testing is entirely up to the legal guardians of the patient, and depends on a variety of personal factors. None of them is systematically linked to overall survival, so it is unlikely that the choice of inclusion criteria led to a biased estimate of the prognostic value of the developed model.

Only a few parameters were preselected for model building; those parameters were selected because they are easily obtainable in a routine setting at the time of diagnosis. End-of-life care (including supportive therapies) can have an impact on overall survival, but within our study, no systematic information about the initiation of

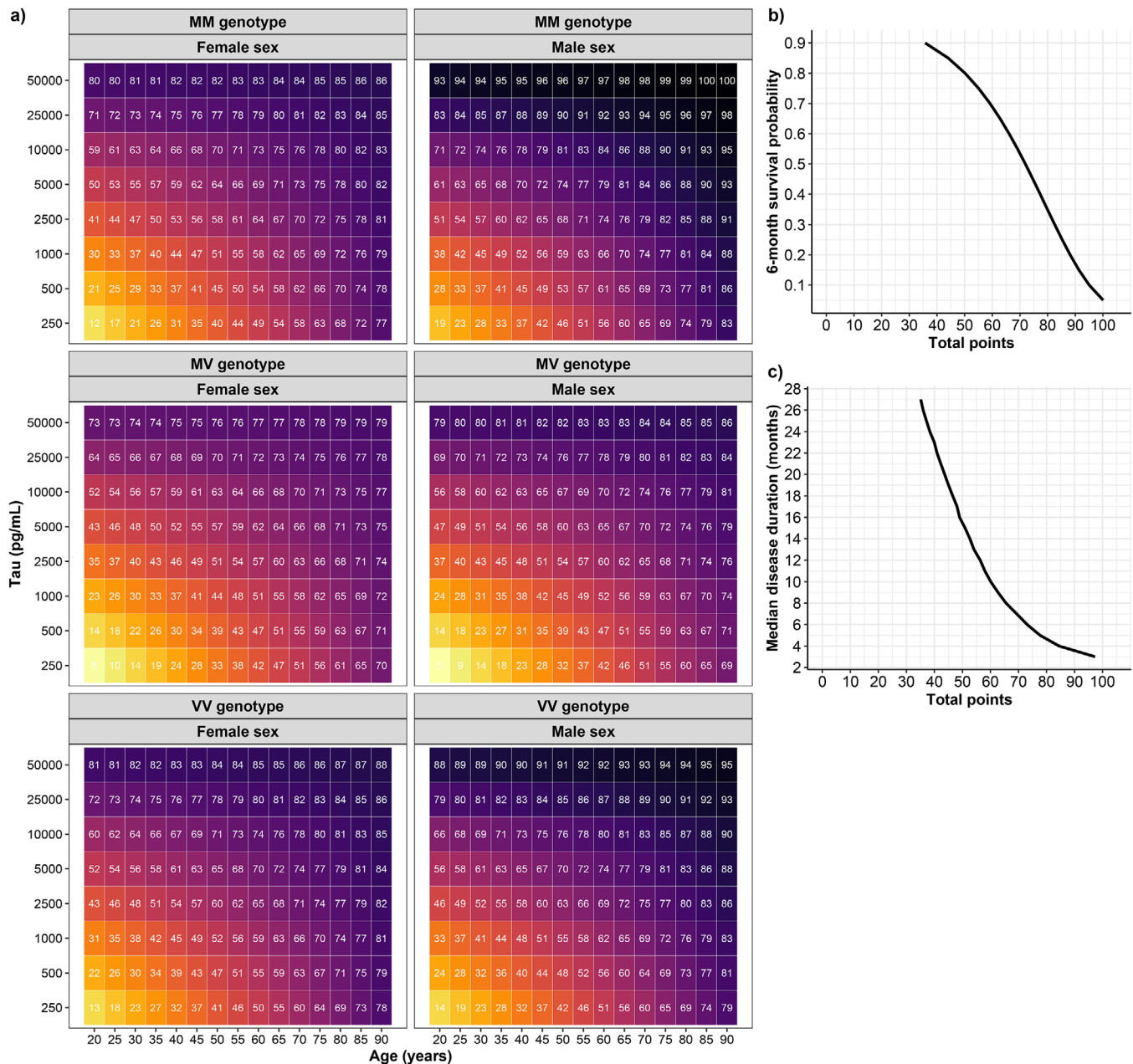


FIGURE 3 Score chart for predicting survival time of sCJD patients. The score chart is used as follows: (a) find out the total points of the patient based on her/his genotype, sex, age, and tau level; determine (b) 6-month survival probability and (c) median survival time (in months) corresponding to the total points

supportive care was collected. Data available at the TSE surveillance unit in Germany suggest that only a small minority of sCJD patients receives supportive care after akinetic mutism. It is unlikely that this could have affected the model-building process because there is no evidence that the decision on end-of-life care is influenced by the variables considered in the model development. No clinical symptoms were taken into account because they are difficult to process; misclassification of symptoms might depend on how the different treating physicians perform physical exams and report their findings. Although magnetic resonance imaging patterns of restricted diffusion and EEG patterns may also be potential predictors of survival time, they

were not included in the model. CSF analyses allowed quantitative evaluation and were performed in one lab in which methods remained unmodified and were continuously controlled during the study period. In contrast, magnetic resonance imaging and EEG were performed externally in most cases. During the study period (1993–2017), technical aspects (scanners, scanning protocols) of these measures changed a lot, precluding a usage of a sufficient number of cases in our model.

Although a previous study reported a stronger association of sCJD survival time with plasma tau than with CSF tau,⁷ we were not able to include plasma tau in our study. However, CSF tau measures used in our study have the advantage of being measured through clinically

validated commercial assays already used in routine care; this is not yet the case for plasma tau. The aim of the present study was to propose a prognostic model for survival in sCJD based on parameters easily obtainable in any neurological tertiary care center. The new ultra-sensitive platforms for quantification of blood-based biomarkers are not yet certified for clinical use, and are not available in all centers. We did not use an independent validation cohort for external validation of our prognostic model because no suitable dataset was available; datasets were either too small, did not include key variables, or were not systematically collected. Steyerberg and Harrell³⁰ stress that both internal and external validation are elaborate tasks and need independent, sufficiently sized datasets with all relevant information. The two steps, therefore, should be kept separate in reporting and publishing. We focused on a thorough internal validation using 10-fold cross-validation instead, providing strong evidence that the model performs well in the setting in which it was developed.

5 | CONCLUSIONS

In summary, we present for the first time a model to predict individual survival time in sCJD patients. It is based on variables easily accessible and routinely collected at the time of diagnosis (age, sex, PRNP genotype, and CSF tau levels). The moderate to good accuracy of the model underlines its usefulness in daily practice, but also provides room for improvement of the model, by including additional parameters (based on imaging, symptoms, or biomarkers), which might currently not be available at all clinical centers. The large cohort of probable and definite sCJD cases used for model development is a strength of our work, as well as the cross-validation approach used for internal validation. By offering a ready-to-use score chart, we provide a valuable tool for clinicians without in-depth knowledge of prognostic models.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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