Hearing recovery for patients with iSSNHL: Development of a prognostic model using UK cohort data

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Key Points

Question:

Can we predict hearing recovery in adults with iSSNHL in ENT clinics to inform treatment decisions?

Findings:

Based upon prospective cohort data of 458 adult patients with iSSNHL from 76 hospitals across the UK, we developed and validated a multivariable prognostic model, showing that initiation of steroid within 7 days from symptom onset, lower severity of hearing loss at presentation to ENT, absence of vertigo, younger age and a history of cardiovascular disease, reliably predict complete hearing recovery.

Meaning:

This prognostic model can help ENT surgeons make informed treatment decisions in patients with iSSNHL. It is available at https://suddenhearingloss.shinyapps.io/recovery

Abstract

Importance

The prognosis of idiopathic sudden onset hearing loss (iSSNHL) is uncertain. This adds to uncertainty in clinical decision making and to the patients' burden of the condition.

Objective

To develop and internally validate a prognostic model for hearing recovery in iSSNHL, with the aim of supporting ENT surgeons in making informed treatment decisions in individual patients with iSSNHL.

Design

The prognostic model was developed using data from the SeaSHeL (Sudden onset Sensorineural Hearing Loss) prospective cohort study, delivered by a research collaborative of 240 ENT trainees, audiologists, foundation doctors and medical students from December 2019 to May 2022.

Setting

ENT departments at 76 NHS hospitals in England and Wales.

Participants

Adult patients, aged over 16 years, diagnosed with iSSNHL.

Intervention(s)

Routine NHS treatment, including oral steroids and intratympanic steroid injections.

Main Outcome(s) and Measure(s)

The primary outcome was complete hearing recovery, defined as return to within 10 dB of pre-onset of iSSNHL hearing levels at all frequencies in the affected ear at 6-16 weeks post symptom onset.

Results

Of the 812 adult patients with iSSNHL recruited in the SeaSHeL cohort between December 2019 and April 2022, 458 (56%) met the criteria for inclusion in the model. Of those, 210 (46%) were classed to have complete hearing recovery.

The following five predictors were found to be independent predictors for complete hearing recovery: steroid treatment within 7 days from symptom onset, lower severity of hearing loss at presentation to ENT, absence of vertigo, younger patient age and a history of cardiovascular disease. The model showed good performance after internal validation: the c-index was 0.77 (95% confidence interval 0.72–0.81). Predictions for complete recovery aligned well with observed complete recovery rates, and greater clinical utility than 'treat all' or 'treat none' strategies was shown.

Conclusion and Relevance

This prognostic model can help ENT surgeons make informed treatment decisions in individual patients with iSSNHL. It is available as a free online tool at https://suddenhearingloss.shinyapps.io/recovery

Introduction

Each year an estimated 20-60 per 100,000 individuals experience sudden sensorineural hearing loss (SSNHL).[1–4] In 90% of these cases no cause is found and a diagnosis of idiopathic SSNHL (iSSNHL) is made.[1,2,5] Patients with iSSNHL have difficulties localising sounds and understanding speech in noisy environments, they may have tinnitus, and poorer quality of life.[6,7] Uncertainty about the prognosis of hearing loss and associated symptoms of iSSNHL adds to patients' distress and anxiety.[8]

Steroids are the treatment of choice for iSSNHL, aiming to reduce peri-insult inflammation within the cochlea.[1,9] The few randomised controlled studies that have compared steroids with placebo or no treatment in iSSNHL have reported spontaneous hearing recovery rates from 15% to 65%, using various definitions of recovery.[1,3,4,9–13] Systematic reviews of these studies also showed large variation in hearing recovery and highlighted the low quality of most of the trials.[14–16] With a potentially favorable natural course of iSSNHL and inconclusive or modest benefits from steroids reported, patients and clinicians need better support in the treatment decisions for iSSNHL.

Several multivariable prognostic studies have been undertaken to evaluate hearing recovery in patients with iSSNHL.[13,17–21] The data for all prognostic studies were collated retrospectively for clinical management purposes and therefore analyses are prone to bias from data missingness. Additionally, all studies were conducted at large city based hospitals and therefore their generalisability across all populations is limited. Three studies did not use the prognostic factors identified to create a prognostic model,[13,18,20] preventing translation into clinical practice. The remaining three did develop prognostic models but did not consistently develop or report their models in line with best practice methods.[17,19,21]

In this study we develop and internally validate a prognostic model for hearing recovery in iSSNHL building on the data of a large prospective cohort of adult patients diagnosed with iSSNHL in ENT clinics across 76 hospitals in England and Wales, with the aim of supporting ENT surgeons in making informed treatment decisions in individual patients with iSSNHL.

Methods

Study design

The prognostic model was developed using data from the SeaSHeL (Sudden onset Sensorineural Hearing Loss) prospective cohort study, delivered by a research collaborative of 240 ENT trainees, audiologists, foundation doctors and medical students from 76 NHS hospitals in England and Wales (NCT04108598), from December 2019 to May 2022.[22] UK Health Research Authority and NHS Research Ethics was obtained, with the study protocol approved by the North West - Greater Manchester East Research Ethics Committee (October 2019, 19/NW/0556). Model development was performed and reported according to the TRIPOD guidelines.[23] Please see Supplement 2 for the completed TRIPOD checklist.

Patient cohort

Inclusion criteria for the SeaSHeL study were adult patients, aged over 16 years, presenting to participating ENT departments at NHS hospitals with a history of sudden hearing loss (within a 72-hour window) that was sensorineural in nature.[22] Most patients presenting with iSSNHL do not have pre-existing hearing tests and so defining their baseline hearing level before the onset of iSSNHL (pre-iSSNHL) is rarely known. This is problematic in making the diagnosis of iSSNHL, as well as measuring recovery to baseline as both require a baseline pre-iSSNHL measure of hearing levels. We used a stepwise strategy to define the baseline pre-iSSNHL hearing level: a) When available we used thresholds from a hearing test pre-iSSNHL, b) If unavailable we used thresholds from the unaffected ear; c) If the unaffected ear had existing hearing loss (≥30dB hearing loss over at least three consecutive frequencies between 250 and 8000 Hz) we used age-adjusted normative thresholds. Hearing loss was

defined as a decrease from this pre-iSSNHL baseline hearing level of ≥30 dB affecting at least three consecutive frequencies between 250 and 8000 Hz.

For this prognostic model, we included patients diagnosed with single sided iSSNHL, with idiopathic defined as SSNHL of unknown cause as determined by the clinician managing the patient. We excluded patients who had a baseline audiogram more than 16 weeks after symptom onset.

All patients underwent routine NHS treatment according to local protocols for iSSNHL, including oral steroids (prednisolone and methylprednisolone of varying doses and regimens) and intratympanic (IT) steroid injections (dexamethasone, prednisolone and methylprednisolone of varying doses and regimens).

Primary outcome measure

The primary outcome of the prediction model was recovery of hearing, dichotomised as 'complete hearing recovery' and 'partial to no hearing recovery'.[1] Complete hearing recovery was defined as the pure tone average (PTA) across six frequencies at 6 to 16 weeks after symptom onset being within 10 dB of the pre-iSSNHL baseline PTA. If the criteria of 'complete hearing recovery' were not met, then the hearing outcome was classed as 'partial to no hearing recovery'.

Patients who had their follow up audiogram prior to 6 weeks from symptom onset (that is no audiometric data between the 6-16 week window) were considered to have outcome data that was missing completely at random and so their outcome data was imputed, see statistical analysis and Supplement 3 for further details.

Predictors for the model were identified through literature review and expert opinion. Nine predictors previously reported as independent prognostic factors for complete recovery of patients with iSSNHL were selected for inclusion in the model. They were: age, gender, presence of tinnitus, presence of vertigo, precipitating illness, pattern of hearing loss, severity of hearing loss, time between onset of symptoms and treatment with steroids (oral or intratympanic), and cardiovascular comorbidity (presence of any of the following: hypertension, hyperlipidaemia, coronary heart disease, heart failure, atrial fibrillation, stroke/TIA and diabetes mellitus). Time between onset of symptoms and treatment with steroids (oral or intratympanic) was categorised into four groups: no treatment, 0 to 7 days, 8 to 14 days, and >14 days. Severity of hearing loss was based on average hearing level across 6 frequency (250-8000hz) and classified as mild (25-40 dB HL), moderate (41-70 dB HL), severe (71-95 dB HL) and profound (>95 dB HL). Pattern of hearing loss was categorised as ascending, descending, flat and irregular audiogram curves according to the classification system by Zhang et al.[17]

Sample size considerations

The minimum sample size for developing a multivariable model[24] to predict complete recovery in patients with SSNHL allowing for 15 parameters to be estimated, assuming a complete recovery of 45%, using a Nagelkerke's R-squared of 0.15, a 0.05 margin of error in estimation of intercept, and a shrinkage factor of ≥0.90, was 380 patients.

Statistical analysis

We used multiple imputation with chained equations to address missing data; analyses were done in each imputed dataset and pooled using Rubin's rules.[25,26] The percentage of cases

with missing data that was imputed was 24% (109 out 458 patients had at least one missing variable). Additional information about handling of missing data can be found in Supplement 3. Multivariable logistic regression was performed to develop the prognostic model. Nonlinear associations between continuous predictors (i.e. age) and recovery were assessed using restricted cubic splines.[27] Plausibility of nonlinear associations was evaluated graphically and benefit for model fit was tested using likelihood-ratio testing. Plausible interaction terms (i.e. severity of hearing loss and vertigo, age and cardiovascular disease) were tested and incorporated if significantly benefitting model fit. Backward selection was used to achieve the most informative and parsimonious combination of predictors. Variables were selected based on Akaike's Information Criterion (AIC). AIC corresponds to significance-based selection at a significance level of $p = 0.157$. Wald $\chi 2$ tests of individual predictors were used.[23] The robustness of the selected model was evaluated using bootstrap resampling with 500 replicates, repeating the variable selection process in each of the bootstrap replicates starting with the initial model including all 9 predictors. Stability of the selected model was evaluated using i) predictor inclusion frequencies to quantify how likely a predictor was selected, and ii) model selection frequencies to quantify how likely a particular set of predictors was selected.[28] We conducted a sensitivity analysis (see Supplement 4) by comparing the results of a model developed using only complete cases (349 patients of whom 109 recovered) to the model developed using multiple imputation.

Internal validation

As prognostic models developed using multivariable regression are at risk of overfitting, the final model with 5 predictors was internally validated using bootstrapping with 500 repetitions. After bootstrapping, model coefficients were adjusted for the degree of

optimism in the model and the model intercept was reassessed after adjustment of model coefficients. Impact of individual predictors was evaluated by estimating odds ratios (ORs) with corresponding 95% confidence interval (CI). Model performance was re-evaluated after internal validation and expressed by discrimination, calibration, and clinical utility (quantified as net benefit). Discrimination was quantified with the concordance (c-) index, which varies between 0.5 for a non-informative model and 1 for a perfectly discriminating model.[29] Calibration refers to the level of agreement between predicted risks and observed outcome and was assessed graphically using a calibration plot. Relative strength of individual predictors was presented graphically using a forest plot including 95% CI of the OR.

Decision curve analysis allows assessment of clinical utility by quantifying the trade-off between correctly identifying true positives and incorrectly identifying false positives weighted according to the threshold probability.[30] The threshold probability represents the risk cutoff above which any given treatment or intervention might be considered and reflects the perceived risk-to-benefit ratio for the intervention. Decision curve analysis was used to quantify the net benefit of implementing the model in clinical practice, compared with various treatment strategies e.g. treat-all approach, a treat-none approach, and a model including the strongest predictor.

Statistical analyses were performed using R (version 4.3.2, Foundation for Statistical Computing, Vienna, Austria) using packages 'rms' and 'mice'.

Results

Of the 812 patients with SSNHL recruited in the SeaSHeL cohort between December 2019 and April 2022, 458 (56%) met the criteria for inclusion in the model. Of those 210 (46% range across imputations 44-47%) had complete hearing recovery. Patient, disease and treatment characteristics are summarised in Table 1. Supplement 5 presents this data in further detail.

Model development and internal validation

The nine predictors (age, gender, presence of tinnitus, presence of vertigo, precipitating illness, pattern of hearing loss, severity of hearing loss, time between onset of symptoms and treatment with steroids, and cardiovascular comorbidity) were included in a multivariable logistic regression model to develop the clinical prognostic model. The use of restricted cubic splines and interaction terms were not found to substantially improve model fit. After backward selection, the following five predictors remained in the multivariable model: age, cardiovascular disease, vertigo, time from onset to first steroid treatment, and severity of hearing loss. The model coefficients and odds ratios are presented in Table 2.

Each of the five predictors were selected in at least 83% (range 83-100%) of the bootstrap samples, and the combination of all five predictors were selected in 74% of the 500 models, a combination of 3 out 5 selected predictors was selected in 99% of the 500 models (Supplement 6).

A shrinkage factor of 0.90 was estimated through bootstrapping in internal validation and applied. The strongest predictor was time from onset to first steroid treatment (within 7 days compared to no treatment (odds ratio (OR) 5.23 (95%CI 2.28 - 11.96)), between 8 and 14 days compared to no treatment OR 2.28 (95%CI 0.86 – 6.04), and after 14 days compared to no treatment OR 0.89 (95%CI 0.34 – 2.32)), followed by severity of hearing loss (moderate compared to mild hearing loss OR 0.58 (95%CI 0.28 - 1.22), severe compared to mild hearing loss OR 0.43 (95%CI 0.20 - 0.94), and profound compared to mild hearing loss OR 0.19 (95%CI 0.08 - 0.47)), then vertigo present at symptom onset (OR 0.56 (95%CI 0.32 – 1.01)), cardiovascular disease (OR 1.84 (95%CI 1.10 – 3.08)), and age (IQR OR 0.64 (95%CI 0.44 - 0.94)).

The relative strength of each individual predictor is presented graphically in Figure 1. After internal validation, the c-index of the prognostic model was 0.77 (95% CI 0.72 - 0.81). The calibration plot of the internally validated prognostic model is presented in Figure 2. Overall, the predictions by the model aligned well with observed complete recovery rates. Decision-curve analysis to examine clinical utility for the model showed higher net benefit than the treat-all, treat-none and a model including the strongest predictor (time to first treatment) only approaches across a range of risk threshold probabilities (Figure 3).

Sensitivity analysis revealed that the same five predictors were selected in the complete cases model. The consistent coefficients and performance metrics across both methods indicate that our model development and predictions were robust to the handling of missing data.

The internally validated prognostic model was incorporated in an online application, which enables personalised prediction of complete recovery in individual patients with SSNHL. The tool shows predicted probabilities of complete recovery within 10 dB of baseline with corresponding confidence intervals and is available as a free online tool at https://suddenhearingloss.shinyapps.io/recovery. The predicted probability of complete recovery for individual patients can also be obtained using the information provided in table 2 footnote. Therefore, this prognostic model can help ENT surgeons make informed treatment decisions in individual patients with iSSNHL.

Discussion

We developed and validated a prognostic model for hearing recovery in adults diagnosed with iSSNHL in NHS ENT clinics. Internal validation showed consistent discrimination, calibration, and net benefit. The model is intended for use in ENT clinics and integrates five routinely available predictors to provide the probability of complete hearing recovery of an individual patient at first diagnosis of iSSNHL. These predictions will support clinicians in informing their patients about the likelihood of hearing recovery and making shared treatment decisions, e.g., initial steroid treatment or secondary salvage treatment for those with a low likelihood of recovery, or long-term hearing rehabilitation (e.g. hearing aids or auditory implants). In shared decisions where the trade-off between possible cure and potential harm of treatment result in decisional uncertainty, our prognostic model demonstrates superiority in net benefit over other strategies such as 'treat all', 'treat none', and 'treat based on a model only using time to treatment'.

Previous studies investigating prognostic factors for iSSNHL corroborate our findings that earlier time to treatment, lower severity of hearing loss at presentation, absence of vertigo and younger patient age are predictors of hearing recovery.[13,17,18,20,21,31] Our study is the first to report that the presence of cardiovascular disease also predicts complete hearing recovery (OR 1.84 (1.10 - 3.08)). This appears counterintuitive but was a stable finding across all our analyses and may relate to anti-inflammatory medications that these patients take or reflect iSSNHL occurring by a different pathological process, and one that is potentially more prone to recovery. Further investigations to confirm and better understand this association are warranted.

The study has some limitations. Some predictor data were missing. This is due to these data being captured in an acute ENT clinical setting where the primary focus is on treatment rather than data recorded specifically for informing research. Second, some of our outcome data were captured before or after the desired 6-16 week follow up window. This may reflect the pressures on the NHS clinical services during the COVID-19 pandemic which occurred during the course of this study. The core study team met regularly to overcome this, verified data accuracy and completeness, and encouraged sites to capture and enter data. Bias during analysis was avoided using multiple imputation, all of which has been described transparently.

We used conventional clinical predictors in this prognostic model. Future model development could integrate novel biomarkers of hearing loss.[32] Our model was developed and validated in the context of current care; predictions should therefore be interpreted as reflecting both baseline risk and potential mitigation through interventions. Ongoing prospective external validation of our model will be required to evaluate model performance in diverse international settings.

Patients underwent routine NHS treatment according to local protocols for iSSNHL, including oral steroids (of varying doses and regimens) and IT steroid injections (of varying doses and regimens). We appreciate that whilst our model integrates five routinely available predictors to support ENT surgeons to predict complete hearing recovery, it is unable to specifically guide on the type of steroid medication, dose and regimen. Importantly, there are some strengths of our study directly related to the natural variations in steroid dose and route administered: Firstly the timing of steroids (<7 days) remains a very strong predictor of recovery, irrespective of dose and route; and secondly, in countries where there are protocols in place that dictate the steroid dose and route based on severity of hearing loss,

it becomes very hard to disentangle the impact of steroid dosing variations from the different chances of recovery in differing severities of hearing loss. Our follow up paper will examine the variations in treatments in more detail.

In 116 out of 458 included patients (25%), baseline hearing level was determined using age-adjusted normative thresholds, since thresholds from a hearing test pre-iSSNHL were not available; and we were unable to use thresholds from the unaffected ear given that the unaffected ear had existing hearing loss. The use of age-adjusted normative thresholds in these cases may impact the accuracy of our outcome data. However, we feel this is also a strength of our methods. Many cases of iSSNHL occur in patients without prior hearing tests. Using the contralateral ear as baseline, dogmatically, introduces the risk of underestimating the severity of loss, especially for those who lose hearing in the better hearing ear. This is an issue that affects all studies of this condition. A robust and transparent strategy of dealing with this missing baseline is required, and rarely reported. We have used a step-wise approach that provides this baseline and accounts for these methodological issues.

In summary, this prognostic model uses readily available clinical predictors to support ENT surgeons to predict complete hearing recovery and inform decision making in individual patients with iSSNHL. The model is available as a free online tool at https://suddenhearingloss.shinyapps.io/recovery

Bibliography

1. Chandrasekhar SS, Tsai Do BS, Schwartz SR, Bontempo LJ, Faucett EA, Finestone SA, et al. Clinical practice guideline: sudden hearing loss (update). *Otolaryngol Head Neck Surg*. 2019;**161**:S1–45
2. Stachler RJ, Chandrasekhar SS, Archer SM, Rosenfeld RM, Schwartz SR, Barrs DM, et al. Clinical practice guideline: sudden hearing loss. *Otolaryngol Head Neck Surg*. 2012;**146**:S1-35
3. Huang G-J, Luo M-S, Lu B-Q, Li S-H. Noninvasive prognostic factors and web predictive tools for idiopathic sudden sensorineural hearing loss. *American Journ of Otolaryngol-Head Neck Med and Surg.* 2023;**44**:103965
4. Wu H, Wan W, Jiang H, Xiong Y. Prognosis of idiopathic sudden sensorineural hearing loss: the nomogram perspective. *Ann Otol Rhinol Laryngol*. 2023;**132**:5–12
5. Marx M, Younes E, Chandrasekhar SS, Ito J, Plontke S, O'Leary S, et al. International consensus (ICON) on treatment of sudden sensorineural hearing loss. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2018;**135**:S23–8
6. Härkönen K, Kivekäs I, Rautiainen M, Kotti V, Vasama JP. Quality of life and hearing eight years after sudden sensorineural hearing loss. *Laryngoscope*. 2017;**127**:927–31
7. Cooper T, Dixit R, Hobson CE, Hirsch BE, McCall AA. Metachronous sudden sensorineural hearing loss: patient characteristics and treatment outcomes. *Otolaryngol Head Neck Surg*. 2020;**162**:337–42
8. Arslan F, Aydemir E, Kaya YS, Arslan H, Durmaz A. Anxiety and depression in patients with sudden one-sided hearing loss. *Ear Nose Throat J*. 2018;**97**:E7

9. National Institute for Health and Care Excellence. Hearing loss in adults: assessment and management. NICE guideline NG98. [Internet]. www.nice.org.uk/guidance/ng98 2018 [accessed 2021 Nov 17].

10. Kuhn M, Heman-Ackah SE, Shaikh JA, Roehm PC. Sudden sensorineural hearing loss: a review of diagnosis, treatment, and prognosis. *Trends Amplif*. 2011;**15**:91–105

11. Mattox DE, Simmons FB. Natural history of sudden sensorineural hearing loss. *Ann Otol Rhinol Laryngol.* 1977;**86**:463–80

12. Conlin AE, Parnes LS. Treatment of sudden sensorineural hearing loss: II. A meta-analysis. *Arch Otolaryngol Head Neck Surg*. 2007;**133**:582–6

13. Kang WS, Yang CJ, Shim M, Song C Il, Kim TS, Lim HW, et al. Prognostic factors for recovery from sudden sensorineural hearing loss: a retrospective study. *J Audiol Otol*: 2017;**21**:9–15

14. Wei BPC, Stathopoulos D, O'Leary S. Steroids for idiopathic sudden sensorineural hearing loss. *Cochrane Database Syst Rev*. 2013;**2**:CD003998

15. Conlin AE, Parnes LS. Treatment of sudden sensorineural hearing loss: I. A systematic review. *Arch Otolaryngol Head Neck Surg* 2007;**133**:573–81

16. Ahmadzai N, Kilty S, Cheng Id W, Id LE, Wolfe Id D, Bonaparte JP, et al. A systematic review and network meta-analysis of existing pharmacologic therapies in patients with idiopathic sudden sensorineural hearing loss. *PLoS One* 2019;**14**:e0221713

17. Zhang S, Li P, Fan F, Zheng Y, Chen X, Chen Y, et al. Nomogram for predicting the prognosis of sudden sensorineural hearing loss patients based on clinical characteristics: a retrospective cohort study. *Ann Transl Med*. 2023;**11**:104–104

18. Edizer DT una, Çelebi Ö, Hamit B, Baki A, Yiğit Ö. Recovery of idiopathic sudden sensorineural hearing loss. *J Int Adv Otol.* 2015;**11**:122–6

19. Yuan H, Liu CC, Ma PW, Chen JW, Wang WL, Gao W, et al. Systemic steroid administration combined with intratympanic steroid injection in the treatment of a unilateral sudden hearing loss prognosis prediction model: A retrospective observational study. *Front Neurol*: 2022;**13**:976393

20. Liu Y, Wu W, Li S, Zhang Q, He J, Duan M, et al. Clinical characteristics and prognosis of sudden sensorineural hearing loss in single-sided deafness patients. *Front Neurol*. 2023;**14**:1230340

21. Čvorović L, Eric D, Probst R, Hegemann S. Prognostic model for predicting hearing recovery in idiopathic sudden sensorineural hearing loss. *Otol Neurotol* 2008;**29**:464–9

22. Mandavia R, Hannink G, Ahmed MN, Premakumar Y, Chu TSM, Blackshaw H, et al. Prognostic factors for outcomes of idiopathic sudden sensorineural hearing loss: protocol for the SeaSHeL national prospective cohort study. *BMJ Open*. 2020;**10**:e038552

23. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMC med*: 2015;**13:**1

24. Riley RD, Ensor J, Snell KIE, Harrell FE, Martin GP, Reitsma JB, et al. Calculating the sample size required for developing a clinical prediction model. *BMJ*: 2020;**368**:m441

25. Wood AM, Royston P, White IR. The estimation and use of predictions for the assessment of model performance using large samples with multiply imputed data. *Biom J*. 2015;**57**:614–32

26. van Buuren S. Flexible imputation of missing data, second edition. Chapman and Hall/CRC: 2018

27. Harrell FE. Regression modeling strategies with applications to linear models, logistic and ordinal regression, and survival analysis. Springer International Publishing: 2015

28. Heinze G, Wallisch C, Dunkler D. Variable selection – a review and recommendations for the practicing statistician. *Biomet Journ*: 2018;**60**:431–49

29. Collins GS, De Groot JA, Dutton S, Omar O, Shanyinde M, Tajar A, et al. External validation of multivariable prediction models: a systematic review of methodological conduct and reporting. *BMC Med Res Methodol*. 2014;**14**:1–11

30. Vickers AJ, van Calster B, Steyerberg EW. A simple, step-by-step guide to interpreting decision curve analysis. *Diagn Progn Res*. 2019;**3**:1–8

31. Yuan H, Liu CC, Ma PW, Chen JW, Wang WL, Gao W, et al. Systemic steroid administration combined with intratympanic steroid injection in the treatment of a unilateral sudden hearing loss prognosis prediction model: A retrospective observational study. *Front Neurol*. 2022;**13**:976393

32. Gomaa NA, Jimoh Z, Campbell S, Zenke JK, Szczepek AJ. Biomarkers for inner ear disorders: scoping review on the role of biomarkers in hearing and balance disorders. *Diagnostics*. 2020;**11**:42

33. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. *Journ of stat soft*. 2011:**45**:1-68.

34. Enders CK. Applied missing data analysis: Guilford press; 2010.

35. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med.* 2011;**30**:377-399.

36. von Hippel PT. How many imputations do you need? A two-stage calculation using a quadratic rule. Sociol Methods Res 2020;**49**:699-718.

Author Contributions

RM, NJ, GH, AS, NM made substantial contributions to the conception and design of the study, analysis and interpretation of data and writing the manuscript. MA, DP, SB, PG, II, JL, made contributions to data acquisition and reviewing the work. All authors have approved the version to be published; and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The SeaSHeL collaborative (see Supplement 1) including ENT trainees, ENT surgeons, audiologists, foundation doctors and medical students from 76 NHS hospitals across the UK, set up the study locally and collected and submitted local data for analysis.

Conflict of Interest Disclosures

No conflicts of interest to report.

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Access to Data and Data Analysis

RM, NM, GH, NJ, AS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Previous Publication/Submissions

This manuscript has not been published previously in print or electronic format and is not under consideration by another publication or electronic medium.

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Table 1: Patient, disease and treatment characteristics related to complete hearing recovery

Variable	Categories	Patients[a] (n)	Complete recovery[a] (n)	Complete recovery[b] (%)	Recovery gradient[c] (% (95% CI))
Patient characteristics					
Age	≤ 48 yrs	120	63	52.5	14.8 (2.4 to 27.2)
	Between 48-71 yrs	216	102	47.2	
	≥ 71 yrs	122	46	37.7	
Sex	Male	243	118	48.4	5.7 (-3.4 to 14.8)
	Female	215	92	42.7	
Ethnicity	White	404	183	45.3	3.6 (-10.6 to 17.8)
	Non-white	54	26	48.9	
Smoking status	Smoker	49	22	44.2	3.5 (-7.1 to 14.1)
	Ex-smoker	119	52	43.5	
	Never smoked	290	136	47.0	
Alcohol consumption	None	159	71	44.7	3.2 (-18.9 to 25.3)
	Moderate	277	128	46.1	
	Hazardous & Harmful	22	11	47.9	
Occupation	Higher occupations	188	83	44.2	12.6 (-12.8 to 38.0)
	Intermediate occupations	94	42	45.0	
	Small employers/own account workers	36	19	53.8	
	Lower supervisory/technical occupations	42	19	46.4	
	Semi-routine/routine occupations	74	36	47.9	
	Never worked/long-term unemployed	25	10	41.2	
Educational level	Primary or less & Secondary	241	115	47.8	4.3 (-4.9 to 13.4)
	Tertiary or further education	217	95	43.5	
Cardiovascular disease	No	289	127	44.0	4.8 (-4.6 to 14.3)
	Yes	169	82	48.8	
Disease characteristics					
Aural fullness	No	381	178	46.7	5.5 (-6.6 to 17.6)
	Yes	77	32	41.2	
Tinnitus	No	202	97	47.9	3.8 (-5.4 to 13.0)
	Yes	256	113	44.1	
Vertigo	No	355	178	50.1	19.2 (8.9 to 29.5)
	Yes	103	32	30.9	
Precipitating illness	No	389	179	45.9	1.2 (-11.5 to 14.0)
	Yes	69	31	44.7	
PTA baseline (dB)	≤ 11.6	111	52	46.8	3.5 (-9.5 to 16.5)
	Between 11.6-28.6	234	109	46.6	
	≥ 28.6 yrs	113	49	43.4	
Pattern of hearing loss	Ascending	33	24	71.3	31.3 (14.3 to 48.4)
	Descending	178	71	40.0	
	Flat	164	72	43.7	
	Irregular	83	43	52.0	
Severity of hearing loss	Mild (25–40 dB)	52	34	64.8	39.4 (23.6 to 55.3)
	Moderate (41–70 dB)	172	91	52.7	
	Severe (71–95 dB)	146	63	43.0	
	Profound (>95 dB)	88	22	25.4	
Treatment characteristics					
Time from onset to first steroid treatment	No steroid treatment	33	7	20.7	40.3 (30.1 to 50.5)
	Within first 7 days	268	159	59.4	

	Between 8 and 14 days	71	27	38.2	
	After 14 days	86	16	19.1	
First steroid treatment	No steroid treatment	33	7	20.7	36.6 (16.8 to 56.3)
	Oral	378	176	46.5	
	IT	47	27	57.4	
Ever IT steroids	No	269	116	43.1	6.4 (-2.8 to 15.7)
	Yes	189	94	49.5	

[a] Pooled number of cases across 100 multiple imputed datasets rounded to the nearest number.
[b] Recovery percentages were calculated using pooled numbers of cases across 100 multiple imputed datasets before rounding.
[c] Recovery gradient represents the difference in complete recovery between highest and lowest rates in each category.

Table 2: Model coefficients and odds ratios for 9 predictors

	Univariable	Multivariable[b]
Variables	**OR (95%CI)**	**OR (95%CI)**
Age[a]	0.71 (0.54 - 0.94)	0.64 (0.44 - 0.94)
Sex		
Male	1 (reference)	-
Female	0.79 (0.54 - 1.16)	-
Cardiovascular disease		
No	1 (reference)	1 (reference)
Yes	1.21 (0.82 - 1.80)	1.84 (1.10 - 3.08)
Tinnitus		
No	1 (reference)	-
Yes	0.86 (0.58 - 1.26)	-
Vertigo		
No	1 (reference)	1 (reference)
Yes	0.44 (0.27 - 0.74)	0.56 (0.32 - 1.01)
Precipitating illness		
No	1 (reference)	-
Yes	0.95 (0.56 - 1.62)	-
Time from onset to first steroid treatment		
No treatment	1 (reference)	1 (reference)
Within 7 days	5.62 (2.31 - 13.71)	5.23 (2.28 - 11.96)
Between 8 and 14 days	2.38 (0.88 - 6.40)	2.28 (0.86 - 6.04)
After 14 days	0.91 (0.33 - 2.51)	0.89 (0.34 - 2.32)
Pattern of hearing loss		
Ascending	1 (reference)	-
Flat	0.31 (0.13 - 0.73)	-
Descending	0.27 (0.12 - 0.62)	-
Irregular	0.44 (0.18 - 1.07)	-
Severity of hearing loss		
Mild (25-40 dB)	1 (reference)	1 (reference)
Moderate (41-70 dB)	0.60 (0.32 - 1.16)	0.58 (0.28 - 1.22)
Severe (71-95 dB)	0.41 (0.21 - 0.80)	0.43 (0.20 - 0.94)
Profound (>95 dB)	0.18 (0.08 - 0.40)	0.19 (0.08 - 0.47)

[a] The odds ratio is the linear interquartile odds ratio (IQR OR), interquartile range for age 48-71 years.

[b]Odds ratios obtained from internally validated model.

The probability (P) of complete recovery after iSSNHL can be obtained as follows: $P_{\text{complete recovery}} = \frac{1}{1+\exp(-LP)}$,

where LP = 0.5260458 + -0.01913038*Age + 0.610793*Cardiovascular disease + -0.5737122*Vertigo + 1.653526*[Treatment within 7 days] + 0.8256298*[Treatment between 8 and 14 days] + -0.1149179*[Treatment after 14 days] + -0.5439007*[Moderate hearing loss (41–70dB)] + -0.8373378*[Severe hearing loss (71–95dB)] + -1.672179*[Profound hearing loss (>95dB)];

[c] = 1 if subject is in group c, 0 otherwise.

An online calculator to estimate complete recovery after iSSNHL is available at https://suddenhearingloss.shinyapps.io/recovery

Figure 1: Graphical representation of relative strength of each individual predictor

Figure 2: Calibration plot of internally validated prognostic model

Figure 3: Decision-curve analysis to examine clinical utility for the model