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ORIGINAL ARTICLE CLINICAL STUDIES

Therapy Intensity Level Scale for Traumatic Brain Injury: Clinimetric Assessment on Neuro-Monitored Patients Across 52 European Intensive Care Units

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Abstract

Intracranial pressure (ICP) data from traumatic brain injury (TBI) patients in the intensive care unit (ICU) cannot be interpreted appropriately without accounting for the effect of administered therapy intensity level (TIL) on ICP. A 15-point scale was originally proposed in 1987 to quantify the hourly intensity of ICP-targeted treatment. This scale was subsequently modified—through expert consensus—during the development of TBI Common Data Elements to address statistical limitations and improve usability. The latest 38-point scale (hereafter referred to as TIL) permits integrated scoring for a 24-h period and has a five-category, condensed version ($TIL^{(Basic)}$) based on qualitative assessment. Here, we perform a total- and component-score analysis of TIL and $TIL^{(Basic)}$ to: 1) validate the scales across the wide variation in contemporary ICP management; 2) compare their performance against that of predecessors; and 3) derive guidelines for proper scale use. From the observational Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study, we extract clinical data from a prospective cohort of ICP-monitored TBI patients ($n = 873$) from 52 ICUs across 19 countries. We calculate daily TIL and $TIL^{(Basic)}$ scores (TIL_{24} and $TIL^{(Basic)}_{24}$, respectively) from each patient's first week of ICU stay. We also calculate summary TIL and $TIL^{(Basic)}$ scores by taking the first-week maximum (TIL_{max} and $TIL^{(Basic)}_{max}$) and first-week median (TIL_{median} and $TIL^{(Basic)}_{median}$) of TIL_{24} and $TIL^{(Basic)}_{24}$ scores for each patient. We find that, across all measures of construct and criterion validity, the latest TIL scale performs significantly greater than or similarly to all alternative scales (including $TIL^{(Basic)}$) and integrates the widest range of modern ICP treatments. TIL_{median} outperforms both TIL_{max} and summarized ICP values in detecting refractory intracranial hypertension (RICH) during ICU stay. The RICH de-

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tection thresholds which maximize the sum of sensitivity and specificity are $TIL_{median} \geq 7.5$ and $TIL_{max} \geq 14$. The TIL_{24} threshold which maximizes the sum of sensitivity and specificity in the detection of surgical ICP control is $TIL_{24} \geq 9$. The median scores of each TIL component therapy over increasing TIL_{24} reflect a credible staircase approach to treatment intensity escalation, from head positioning to surgical ICP control, as well as considerable variability in the use of cerebrospinal fluid drainage and decompressive craniectomy. Since $TIL^{(Basic)}_{max}$ suffers from a strong statistical ceiling effect and only covers 17% (95% confidence interval [CI]: 16–18%) of the information in TIL_{max}, $TIL^{(Basic)}$ should not be used instead of TIL for rating maximum treatment intensity. $TIL^{(Basic)}_{24}$ and $TIL^{(Basic)}_{median}$ can be suitable replacements for TIL_{24} and TIL_{median}, respectively (with up to 33% [95% CI: 31–35%] information coverage) when full TIL assessment is infeasible. Accordingly, we derive numerical ranges for categorising TIL_{24} scores into $TIL^{(Basic)}_{24}$ scores. In conclusion, our results validate TIL across a spectrum of ICP management and monitoring approaches. TIL is a more sensitive surrogate for pathophysiology than ICP and thus can be considered an intermediate outcome after TBI.

Keywords: clinimetrics; intensive care unit; intracranial pressure; Therapy Intensity Level; traumatic brain injury; validation.

Introduction

Elevated intracranial pressure (ICP) following traumatic brain injury (TBI) may impede the potential recovery of injured brain tissue and damage initially unaffected brain regions.[1] Therefore, for TBI patients admitted to the intensive care unit (ICU), clinicians often monitor ICP and apply a wide range of ICP-reducing treatments.[2] The selective use of these treatments typically follows a staircase approach, in which therapeutic intensity—defined by the risk and complexity of each treatment—is incrementally escalated until adequate ICP control is achieved.[3-5] Thus, therapeutic intensity must be considered when interpreting ICP. Even if two TBI patients have comparable ICP values, a difference in the intensity of their ICP-directed therapies likely indicates a difference in pathophysiological severity.

Several versions of the Therapy Intensity Level (TIL) scale have been developed to rate and compare the overall intensity of ICP management amongst TBI patients. TIL scales assign a relative intensity score to each ICP-targeting therapy and return either the sum or the maximum value of the scores of simultaneously applied therapies. In 1987, Maset and colleagues produced the original, 15-point TIL scale ($TIL^{(1987)}$) to be assessed once every 4 h.[6] In 2006, Shore and colleagues published the 38-point Pediatric Intensity Level of Therapy (PILOT) scale,[7] revising $TIL^{(1987)}$ to: 1) represent updated pediatric TBI management practices; 2) have a more practical, daily assessment frequency; and 3) resolve a statistical ceiling effect. In 2011, the inter-agency TBI Common Data Elements (CDE) scheme developed the most recent, 38-point TIL scale (hereafter referred to as TIL) as well as a condensed, five-category $TIL^{(Basic)}$ scale through expert consensus.[8] The TIL scale revised PILOT to integrate additional ICP-directed therapies and to be applicable to adult TBI management. Moreover, $TIL^{(Basic)}$ was proposed as a simple, categorical measure to use when full TIL assessment would be infeasible. Since Zuercher and colleagues reported the validity and reliability of TIL in a two-center cohort ($n = 31$) in 2016,[9] the scale has become a popular research metric for quantifying ICP treatment intensity.[10–13]

However, several critical questions regarding TIL remain unanswered. It is uncertain whether the validity of TIL, reported in a relatively small population, can be generalized across the wide variation of ICP management, monitoring, and data acquisition (i.e., intermittent chart recording or high-resolution storage)[14] strategies practiced in contemporary intensive care.[11,12,15,16] Further, the scoring configuration of TIL has never been tested against alternatives (e.g., $TIL^{(1987)}$ and PILOT), and the relative contribution of TIL's component therapies towards the total score is unknown. It is unclear how $TIL^{(Basic)}$ numerically relates to TIL and if the former captures the essential information of the latter. In this work, we aimed to answer these questions by performing a comprehensive assessment of TIL on a large, contemporary population of ICP-monitored TBI patients across European ICUs.

Methods

Therapy Intensity Level (TIL) and alternative scales

TIL refers to the 38-point scale developed by the CDE scheme for TBI.[8] The domain or construct (i.e., targeted concept of a scale) of TIL is the therapeutic intensity of ICP management. The TIL scale has 12 items, each representing a distinct ICP-targeting treatment from one of eight modalities, as defined in Table 1. TIL was developed by an international expert panel, which discussed: 1) the relevant ICP-treatment modalities of modern intensive care; 2) the relative risk and efficacy of individual therapies to derive scores; and 3) practical and statistical limitations of previous TIL scores.[8] In this way, TIL is a formative measurement model in which the construct (i.e., ICP treatment intensity) is not unidimensional but

Table 1. Scoring Configurations for TIL and Alternative Scales

ICP-treatment modality	Item / Sub-item	TIL Score	TIL Max	uwTIL Score	uwTIL Max	$TIL^{(Basic)a}$ Score[a]	$PILOT^{b}$ Score	$PILOT^{b}$ Max	$TIL^{(1987)b}$ Score	$TIL^{(1987)b}$ Max
Positioning	Head elevation for ICP control or nursed flat (180°) for CPP management	1	1	1	1	1	–	–	–	–
Sedation and neuromuscular blockade	Sedation		5		3			5		4
	Low dose sedation (as required for mechanical ventilation).	1		1		1	1		1	
	Higher dose sedation for ICP control (but not aiming for burst suppression).	2		2		2	1		1	
	High dose propofol or barbiturates for ICP control (metabolic suppression).	5		3		4	5		4	
	Neuromuscular blockade (paralysis).	3	3	1	1	–	2	2	1	1
CSF drainage	CSF drainage volume		3		2			5		2
	Low (<120 mL/24h)	2		1		2	4		1	
	High (≥120 mL/24h)	3		2		3	5		2	
CPP management	Fluid loading for maintenance of cerebral perfusion.	1	1	1	1	2	–	–	–	–
	Vasopressor therapy required for management of cerebral perfusion.	1	1	1	1	2	2	2	–	–
Ventilatory management	Hypocapnia for ICP control (P_aCO_2 [mm Hg])		4		3			4		2
	Mild ($35 \le P_aCO_2 < 40$)	1		1		2	1		1	
	Moderate ($30 \le P_aCO_2 < 35$)	2		2		3	2		1	
	Intensive ($P_aCO_2 < 30$)	4		3		4	4		2	
Hyperosmolar therapy	Mannitol administration		3		2			3		6
	≤2g/kg/24h	2		1		2	2		3	
	>2g/kg/24h	3		2		3	3		6	
	Hypertonic saline administration		3		2			3	–	–
	≤0.3g/kg/24h	2		1		2	3			
	>0.3g/kg/24h	3		2		3	3			
Temperature control	Temperature control (T [°C])		5		3			5	–	–
	Fever control (>38 or spontaneous <34.5).	1		1			1			
	Cooling for ICP control (≥35)	2		2		3	3			
	Hypothermia (<35).	5		3		4	5			
Surgery for intracranial hypertension	Intracranial operation for progressive mass lesion, NOT scheduled on admission.	4	4	1	1	4	4	4	–	–
	Decompressive craniectomy.	5	5	1	1	4	5	5	–	–
Maximum total possible score			38		21	4		38		15

The TIL scale was developed by Maas and colleagues.[8] For each calendar day, the highest score for each item was summed to derive the TIL score.

[a]$TIL^{(Basic)}$ is the maximum score (up to 4) among all administered sub-items over the calendar day. If no sub-items are administered on a given day, $TIL^{(Basic)} = 0$.

[b]PILOT scale[7] and $TIL^{(1987)}$ scale[6] scoring configurations have been adapted with minor adjustments to fit the items of TIL with a daily assessment frequency.

CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; ICP, intracranial pressure; P_aCO_2, partial pressure of carbon dioxide in arterial blood; PILOT, Pediatric Intensity Level of Therapy scale[7]; T, body temperature in degrees Celsius; TIL, Therapy Intensity Level scale[8,9]; $TIL^{(1987)}$, original Therapy Intensity Level scale published in 1987[6]; $TIL^{(Basic)}$, condensed TIL scale[8]; uwTIL, unweighted TIL scale in which sub-item scores are replaced by the ascending rank index within the item.

rather defined by the combination of items (i.e., ICP-targeting treatments).[17] TIL was shown to have high inter-rater and intra-rater reliability by Zuercher and colleagues.[9] If a decompressive craniectomy was performed as a last resort for refractory intracranial hypertension, its score was included in the day of the operation and in every subsequent day of ICU stay. TIL scores can be calculated as frequently as clinically desired. For our analysis, we calculated the following TIL scores from the first 7 days of ICU stay:

- TIL_{24}, the daily TIL score based on the sum of the highest scores per item per calendar day,
- TIL_{max}, the maximum TIL_{24} over the first week of a patient's ICU stay,
- TIL_{median}, the median TIL_{24} over the first week of a patient's ICU stay.

We also calculated scores from four other therapeutic intensity scales to compare with TIL scores. The 21-point, unweighted TIL (uwTIL) scale replaces each sub-item score in TIL with its ascending rank index (i.e., 1, 2, 3, …) within each item (Table 1). The five-category $TIL^{(Basic)}$ was also developed by the CDE scheme for TBI and takes the maximum score, from zero (i.e., no ICP-related intervention) to four, amongst all included sub-items over the calendar day.[8] We adapted the 38-point PILOT[7] and 15-point $TIL^{(1987)}$ scales[6] with minor adjustments to fit the items of TIL with a daily assessment frequency. PILOT also was shown to have high inter-rater and intra-rater reliability by Shore and colleagues.[7] For the four alternative scales, daily (i.e., $uwTIL_{24}$, $TIL^{(Basic)}{}_{24}$, $PILOT_{24}$, and $TIL^{(1987)}{}_{24}$), maximum (i.e., $uwTIL_{max}$, $TIL^{(Basic)}{}_{max}$, $PILOT_{max}$, and $TIL^{(1987)}{}_{max}$), and median (i.e., $uwTIL_{median}$, $TIL^{(Basic)}{}_{median}$, $PILOT_{median}$, and

$TIL^{(1987)}_{median}$) scores were calculated in the same way as TIL_{24}, TIL_{max}, and TIL_{median}, respectively.

Study design and populations

Our study population was prospectively recruited for the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) core and high-resolution studies. CENTER-TBI is a longitudinal, observational cohort study (NCT02210221) involving 65 medical centers across 18 European countries and Israel. Patients were recruited between December 19, 2014, and December 17, 2017, if they met the following criteria: 1) presentation within 24 h of a TBI; 2) clinical indication for a CT scan; and 3) no severe pre-existing neurological disorder. In accordance with relevant laws of the European Union and the local country, ethical approval was obtained for each site, and written informed consent by the patient or legal representative was documented electronically. The list of sites, ethical committees, approval numbers, and approval dates can be found online at https://www.center-tbi.eu/project/ethical-approval. The project objectives and design of CENTER-TBI have been described in detail previously.[18,19]

In this work, we applied the following inclusion criteria in addition to those of CENTER-TBI (Fig. 1): 1) primary admission to the ICU; 2) at least 16 years old at ICU admission; 3) invasive ICP monitoring; 4) no decision to withdraw life-sustaining therapies (WLST) on the first day of ICU stay; and 5) daily assessment of TIL.

For our sub-studies evaluating the association between TIL and ICP-derived values, we created two sub-populations based on the type of ICP values available. Patients with end-hour ICP (ICP_{EH}) values, which were recorded by clinicians at the end of every other hour, constituted the TIL-ICP_{EH} sub-population. Patients with high-resolution ICP values (ICP_{HR}), which were automatically stored with monitoring software, constituted the TIL-ICP_{HR} sub-population. All patients in the TIL-ICP_{HR} sub-population were also members of the TIL-ICP_{EH} sub-population (Fig. 1).

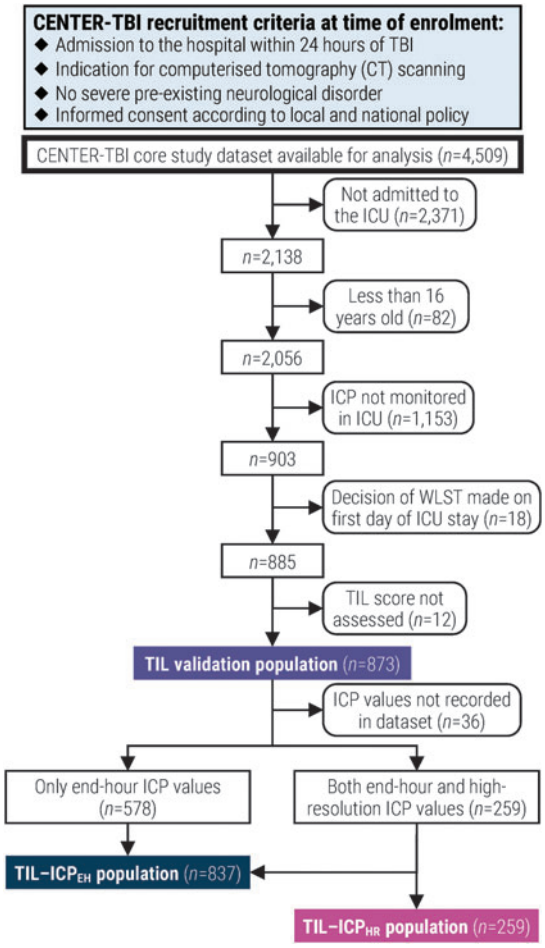


FIG. 1. Flow diagram for patient enrollment and validation population assignment. CENTER-TBI, Collaborative European NeuroTrauma Effectiveness Research in TBI; ICP, intracranial pressure; ICP_{EH}, end-hour ICP; ICP_{HR}, high-resolution ICP; ICU, intensive care unit; TBI, traumatic brain injury; TIL, Therapy Intensity Level scale[8,9]; WLST, withdrawal of life-sustaining therapies.

Data collection

Data for the CENTER-TBI study was collected through the QuesGen electronic case report form system (QuesGen Systems Inc, Burlingame, CA, USA) hosted on the International Neuroinformatics Coordinating Facility (INCF) platform (INCF, Stockholm, Sweden). All data for the validation populations, except high-resolution signals, were extracted from the CENTER-TBI core study[19] (v3.0, ICU stratum) using Opal database software.[20]

ICP management data for TIL calculation

Since TIL_{24} was found to be a reliable summary of hourly TIL,[9] clinical data pertinent to the component items of TIL (i.e., ICP-guided treatments, Table 1) were recorded daily through the first week of ICU stay. We extracted all daily TIL item values for our population, and calculated TIL_{24}, $uwTIL_{24}$, $TIL^{(Basic)}_{24}$, $PILOT_{24}$, and $TIL^{(1987)}_{24}$ as defined in Table 1. For patients who underwent WLST after the first day of ICU stay, we only extracted TIL item information from before the documented date of WLST decision.

ICP_{EH} and related values

End-hour ICP (ICP_{EH}), systolic blood pressure (SBP_{EH}), and diastolic blood pressure (DBP_{EH}) were recorded by clinicians every 2 h for the TIL-ICP_{EH} sub-population. Mean arterial pressure (MAP_{EH}) was calculated as $MAP_{EH} = (SBP_{EH} + 2DBP_{EH})/3$, and cerebral perfusion

pressure (CPP_{EH}) was calculated as $CPP_{EH} = MAP_{EH} - ICP_{EH}$. From ICP_{EH} and CPP_{EH}, we calculated the following values:

- ICP_{24} or CPP_{24}, the mean ICP or CPP value over a calendar day of ICU stay,
- ICP_{max} or CPP_{min}, the maximum ICP_{24} or minimum CPP_{24} value over the first week of a patient's ICU stay,
- ICP_{median} or CPP_{median}, the median ICP_{24} or CPP_{24} value over the first week of a patient's ICU stay.

ICP_{HR} and related values

High-resolution signals were collected using either ICM+ software (Cambridge Enterprise Ltd, Cambridge, U.K.; http://icmplus.neurosurg.cam.ac.uk), Moberg CNS monitor (Moberg Research Inc, Ambler, PA, USA; https://www.moberg.com), or both. Blood pressure was obtained through arterial lines connected to pressure transducers. High-resolution ICP (ICP_{HR}) was acquired from either an intraparenchymal strain gauge probe (Codman ICP MicroSensor, Codman and Shurtleff Inc., Raynham, MA, USA), a parenchymal fiber optic pressure sensor (Camino ICP Monitor, Integra Life Sciences, Plainsboro, NJ, USA; https://www.integralife.com/), or an external ventricular drain. Detailed data collection and pre-processing methods (i.e., artefact cleaning and down-sampling to ten-second averaged time series) applied to high resolution signals in our study have been described previously.[21] Ten-second averaged ICP (ICP_{HR_10sec}) and CPP (CPP_{HR_10sec}) time-series were retrieved for this analysis, and, from ICP_{HR_10sec} and CPP_{HR_10s}, we calculated ICP_{24}/CPP_{24}, ICP_{max}/CPP_{min}, and ICP_{median}/CPP_{median} as described above.

Physician impressions

Attending ICU physicians were asked to record their daily concerns with the patient's ICP and CPP, separately, on a scale from 1 (not concerned) to 10 (most concerned). Moreover, on each patient's ICU discharge summary, physicians were asked to record whether the patient experienced refractory intracranial hypertension during his or her ICU stay. Refractory intracranial hypertension was defined as recurrent, sustained (i.e., of at least 10 min) increases of ICP above 20 mm Hg despite medical ICP management. We extracted the daily ICP/CPP concern ratings and refractory intracranial hypertension impressions which coincided with the ICU stays of our population.

Baseline characteristics, prognosis, and outcome

We extracted baseline demographic characteristics, Marshall CT classifications,[22] and Glasgow Coma Scale (GCS)[23] scores from ICU admission.[24] We also extracted Glasgow Outcome Scale—Extended (GOSE) functional outcome scores at 6 months post-injury,[25] with imputation of missing values as previously described.[26] Finally, we extracted ordinal functional outcome prognosis scores, calculated from a tokenized embedding of all available clinical information in the first 24 h of ICU stay, as described previously.[27]

Validation

We appraised the validity of TIL according to recommendations of best practice from clinimetric literature.[28] Based on the identified domain of TIL, we evaluated the construct and criterion validities of TIL. Our qualitative and quantitative assessments of TIL were performed against those of alternative scoring configurations (Table 1) for comparison.

Construct validity

Construct validity is the extent to which a clinical scale matches expectations of associations with parameters within or outside the identified domain. Construct validity is further broken down into convergent validity (i.e., associations with similar constructs), discriminant validity (i.e., associations with divergent constructs), and differentiation by known groups. In this work, statistical associations between study variables were measured with:

- Spearman's correlation coefficients (ρ) for static (i.e., measured once) variables,
- repeated measures correlation coefficients (r_{rm})[29]—interpreted as within-individual strength of association—for longitudinal (i.e., measured over time) variables,
- linear mixed effects regression (LMER) coefficients (β_{LMER}) of daily scale scores (e.g., TIL_{24}) when regressing ICP_{24} or CPP_{24} on daily scale scores and the day of ICU stay (Day_{ICU}), accounting for inter-patient variability with random intercepts. Therefore, β_{LMER} were interpreted as the expected difference in ICP_{24} or CPP_{24} per unit increase of daily scale score, independent of time since ICU admission or inter-patient variation.

For convergent validity, we expected therapeutic intensity to correlate at least mildly (i.e., $|\rho| \geq 0.2$, $|r_{rm}| \geq 0.2$, $|\beta_{LMER}| > 0$) with markers of injury severity (i.e., baseline GCS and baseline outcome prognoses), functional outcome (i.e., six-month GOSE), clinical concerns of ICP status, and ICP itself. Accordingly, we calculated: 1) ρ values between TIL_{max} and GCS, ordinal prognosis scores, GOSE, and ICP_{max}; 2) ρ values between TIL_{median} and GCS, ordinal prognosis scores, GOSE, and ICP_{median}; 3) r_{rm} values between TIL_{24} and physician concern of ICP and ICP_{24}; and 4) β_{LMER} of TIL_{24} when regressing ICP_{24} on Day_{ICU} and TIL_{24} (i.e., $ICP_{24} \sim Day_{ICU} + TIL_{24}$),

accounting for inter-patient variability with random intercepts.

For discriminant validity, we expected therapeutic intensity to be more strongly correlated with ICP and physician concerns of ICP than with CPP and physician concerns of CPP, respectively. Even though CPP control through fluid loading or vasopressor therapy is a component modality of TIL (Table 1), we expected TIL to capture ICP management (i.e., the construct) more accurately than CPP management. We compared: 1) ρ values of TIL_{max} versus CPP_{min} to those of TIL_{max} vs. ICP_{max}; 2) ρ values of TIL_{median} versus CPP_{median} to those of TIL_{median} vs. ICP_{median}; 3) r_{rm} values of TIL_{24} versus CPP_{24} to those of TIL_{24} vs. ICP_{24}; and 4) the β_{LMER} of TIL_{24} when regressing $CPP_{24} \sim Day_{ICU} + TIL_{24}$ to the β_{LMER} of TIL_{24} when regressing $ICP_{24} \sim Day_{ICU} + TIL_{24}$.

For differentiation by known groups, we expected TIL_{max} and TIL_{median} to effectively discriminate patients who experienced refractory intracranial hypertension during ICU stay from those who did not. We calculated the area under the receiver operating characteristic curve (AUC), which, in our case, was interpreted as the probability of a randomly selected patient with refractory intracranial hypertension having a higher TIL_{max} or TIL_{median} score than one without it. We also compared the AUCs of TIL_{max} and TIL_{median} to ICP_{max} and ICP_{median} and determined the sensitivity and specificity of refractory intracranial hypertension detection at each threshold of TIL_{max} and TIL_{median}.

Criterion validity

Criterion (or concurrent) validity is the degree to which there is an association between a clinical scale and other scales measuring the same construct, particularly a gold standard assessment. Since there is no extant ''gold standard'' for assessing ICP management intensity, we tested the concurrent criterion validity of TIL by calculating its associations with its predecessors (i.e., PILOT and $TIL^{(1987)}$), mindful of their limitations as described above. More specifically, we calculated: 1) ρ values between TIL_{max} and prior scale maximum scores (i.e., $PILOT_{max}$ and $TIL^{(1987)}{}_{max}$); 2) ρ values between TIL_{median} and prior scale median scores (i.e., $PILOT_{median}$ and $TIL^{(1987)}{}_{median}$); and 3) r_{rm} between TIL_{24} and prior scale daily scores (i.e., $PILOT_{24}$ and $TIL^{(1987)}{}_{24}$).

Component item analysis

We evaluated inter-item (i.e., inter-treatment) and adjusted item-total associations of TIL_{24}, $uwTIL_{24}$, $PILOT_{24}$, and $TIL^{(1987)}{}_{24}$ by calculating r_{rm} values. Item-total correlations were adjusted by subtracting the tested item score from the total score prior to calculating the correlation. We measured Cronbach's alpha (α) to assess internal reliability amongst scale items at each day of ICU stay. Moreover, we calculated the median score contribution of each item per total TIL_{24} score. The association between each TIL_{24} item score and ICP_{24}, CPP_{24}, physician concern of ICP, and physician concern of CPP was calculated with r_{rm} values. Finally, we trained LMER models regressing ICP_{24} and CPP_{24} on all TIL items (with categorical dummy encoding) and Day_{ICU} concurrently. The β_{LMER} values from these models were interpreted as the average change in ICP_{24} or CPP_{24} associated with each treatment when accounting for all other ICP-guided treatments, time since ICU admission, and inter-patient variability with random intercepts.

$TIL^{(Basic)}$ information coverage

We examined the distributions of $TIL^{(Basic)}{}_{24}$ per TIL_{24} and TIL_{24} per $TIL^{(Basic)}{}_{24}$ to derive thresholds for categorizing TIL_{24} into $TIL^{(Basic)}{}_{24}$. We also calculated the information coverage (IC) of $TIL^{(Basic)}$ by dividing the mutual information (MI) of $TIL^{(Basic)}$ and TIL by the entropy of TIL. IC was calculated with $TIL^{(Basic)}{}_{24}$ and TIL_{24} for days one through seven of ICU stay, with $TIL^{(Basic)}{}_{max}$ and TIL_{max}, and with $TIL^{(Basic)}{}_{median}$ and TIL_{median}.

Statistical analysis

Multiple imputation of missing values. Five of the static study variables had missing values for some of the patients in our study: GCS, GOSE, baseline prognosis scores, Marshall CT classifications, and refractory intracranial hypertension status. We assessed the patterns of missingness (Supplementary Fig. S1) and multiply imputed ($m = 100$) these variables with independent, stochastic predictive mean matching functions using the mice package[30] (v3.9.0) in R (v4.2.3). We assumed these variables to be missing-at-random (MAR; as previously reported on CENTER-TBI data)[31] and supported this assumption by training imputation models on all study measures as well as correlated auxiliary variables (e.g., raised ICP during ICU stay).

For daily longitudinal study variables, we considered a value to be missing if the patient was still in the ICU and WLST had not been decided on or before that day. We assessed the longitudinal patterns of missingness (Supplementary Fig. S2) and multiply imputed ($m = 100$) these variables with the multivariate, time-series algorithm from the *Amelia II* package[32] (v1.7.6) in R over the first week of ICU stay. The algorithm exploits both between-variable and within-variable correlation structures over time to stochastically impute missing time series values in independently trained runs. We validated the MAR assumption by identifying characteristics significantly associated with longitudinal variable missingness (Supplementary Table S1) and included

auxiliary information associated with value missingness (e.g., reasons for stopping ICP monitoring) in the imputation model.

Statistical inference. We calculated 95% confidence intervals (CI) for ρ, r_{rm}, β_{LMER}, AUC, sensitivity, specificity, α, and IC values using bootstrapping with 1000 resamples of unique patients. For each resample, one of the 100 missing value imputations was randomly chosen. Therefore, confidence intervals represented the uncertainty due to patient resampling and missing value imputation.

Code availability

All statistical analyses were performed in Python (v3.8.2) or R, and all visualizations were created in R. All scripts used in this study are publicly available on GitHub: https://github.com/sbhattacharyay/CENTER-TBI_TIL.

Results

Study population

Of the 4509 patients available for analysis in the CENTER-TBI core study, 873 patients from 52 ICUs met the additional inclusion criteria of this work. Amongst them, 837 constituted the TIL-ICP_{EH} sub-population and 259 constituted the TIL-ICP_{HR} sub-population (Fig. 1). Summary characteristics of the overall population as well as those of the TIL-ICP_{EH} and TIL-ICP_{HR} sub-populations are detailed in Table 2. Apart from two of the prognosis scores pertaining to the probability of returning to pre-injury life roles (i.e., Pr(GOSE >5) and Pr(GOSE >6)), none of the tested characteristics were significantly different between patients in the TIL-ICP_{HR} sub-population and those outside of it (Table 2).

The median ICU stay duration of our population was 14 days (IQR: 7.8–23 days), and 83% ($n = 726$) stayed through at least seven calendar days. At each day of ICU stay, less than 2.4% of the expected TIL scores were missing (Supplementary Fig. S2). Each TIL component item (Table 1) is represented by at least 17% ($n = 147$, intracranial surgery) and each sub-item is represented by at least 4.9% ($n = 43$, high-dose mannitol) of the population (Supplementary Table S2). The distributions of TIL_{max}, TIL_{median}, and TIL_{24}, juxtaposed against the scores of alternative scales (Table 1), are displayed in Figure 2. The distributions of TIL and PILOT were visually similar, and $TIL^{(Basic)}{}_{max}$ had a strong ceiling effect (i.e., 57% of the population had the maximum score). Whilst there was no significant difference in TIL_{24} distribution over the first seven days, most patients had their highest TIL_{24} (i.e., TIL_{max}) soon after ICU admission (median: day two, IQR: days one–three). The Spearman's rank correlation coefficient (ρ) between TIL_{max} and TIL_{median} was 0.80 (95% CI: 0.77–0.82), and the median TIL_{median}:TIL_{max} ratio was 0.65 (IQR: 0.45–0.80).

Validation of TIL

The 95% CIs of ρ values, repeated measures correlation coefficients (r_{rm}), and linear mixed effect regression coefficients (β_{LMER}) of TIL with other study measures are visualized in Fig. 3. Both TIL_{max} and TIL_{median} had mildly negative correlations ($-0.26 < \rho_{mean} < -0.19$) with baseline GCS, six-month GOSE, and functional outcome prognoses (Fig. 3A, 3B). The within-individual association of TIL_{24} with physician concerns of ICP was moderately positive ($r_{rm} = 0.35$ [95% confidence interval [CI]: 0.31-0.38]) and significantly higher than that of $TIL^{(Basic)}{}_{24}$ (Fig. 3C). The association between ICP_{median} and TIL_{median} was moderately positive ($0.35 < \rho_{mean} < 0.45$) with both ICP_{EH} and ICP_{HR} values, and the association between ICP_{max} and TIL_{max} was moderately positive ($\rho = 0.41$ [95% CI: 0.33-0.46]) with ICP_{EH} values. The ICP_{max} vs. TIL_{max} correlation was not significant ($\rho = 0.01$ [95% CI: -0.16-0.17]) with ICP_{HR} values; however, without imputing missing ICP_{HR} values, the ρ was 0.43 (95% CI: 0.35-0.50). This suggests that the longitudinal missingness of ICP_{HR} (Supplementary Fig. S2) for our sample size made the ICP_{max} estimation significantly imprecise. Additionally, the within-individual association with ICP_{24} was either weak or not significant for any daily scale score according to r_{rm} (Fig. 3C) and β_{LMER} (Fig. 3D) values. On average, a single point increase in TIL_{24} was associated with a 0.22 (95% CI: 0.15–0.30) mm Hg increase in daily mean ICP_{EH} and a 0.19 (95% CI: -0.06-0.43) mm Hg increase in daily mean ICP_{HR}. These results mostly affirm the convergent validity of TIL but highlight the broad intra-patient variability between ICP and therapeutic intensity. From the distribution of ICP_{24} values at each TIL_{24} score (Fig. 4A), we observed both considerable ICP_{24} overlap across each TIL_{24} score and an overall positive relationship between TIL_{24} and ICP_{24}, particularly for $TIL_{24} \geq 8$.

The correlation between TIL and both prior scales (i.e., PILOT and $TIL^{(1987)}$) was positively strong for maximum, median, and daily scores (Supplementary Fig. S3), establishing the criterion validity of TIL. According to 95% CIs, the association of TIL with prior scales was stronger than that of uwTIL or $TIL^{(Basic)}$ (Supplementary Fig. S3).

According to ρ, r_{rm}, and β_{LMER} values (Fig. 3), the associations of TIL with CPP and of TIL with physician concerns of CPP were weaker than or not significantly different from the corresponding associations with ICP. Moreover, the trend of CPP_{24} distributions over different TIL_{24} scores is not as visually apparent as that of ICP_{24} distributions over different TIL_{24} scores (Fig. 4B). These results support the discriminant validity of TIL.

In our population, 157 patients (18% of 864 assessed) were reported to experience refractory intracranial hypertension during ICU stay. TIL_{max} correctly discriminated

Table 2. Summary Characteristics of Study Validation Populations

	TIL validation population			
Summary characteristic	*Overall (n = 873, 52 centers)*	*TIL-ICP$_{EH}$ (n = 837, 51 centers)*	*TIL-ICP$_{HR}$ (n = 259, 21 centers)*	*p value[c]*
Age [years]	47 (29–62)	47 (29–62)	48 (30–62.5)	0.303
Sex: Female	222 (25%)	213 (25%)	55 (21%)	0.078
Baseline GCS ($n^a = 822$)				0.554
Mild [13–15]	122 (15%)	115 (15%)	38 (16%)	
Moderate [9–12]	139 (17%)	133 (17%)	36 (15%)	
Severe [3–8]	561 (68%)	539 (68%)	170 (70%)	
Marshall CT ($n^a = 710$)				0.278
No visible pathology (I)	17 (2%)	16 (2%)	6 (3%)	
Diffuse injury II	264 (37%)	248 (36%)	75 (35%)	
Diffuse injury III	93 (13%)	89 (13%)	22 (10%)	
Diffuse injury IV	16 (2%)	16 (2%)	3 (1%)	
Mass lesion (V & VI)	320 (45%)	312 (46%)	107 (50%)	
Six-month GOSE ($n^a = 761$)				0.329
(1) Death	199 (26%)	195 (26%)	54 (23%)	
(2 or 3) Vegetative or lower SD	182 (24%)	181 (25%)	63 (27%)	
(4) Upper SD	70 (9%)	66 (9%)	22 (9%)	
(5) Lower MD	122 (16%)	117 (16%)	44 (19%)	
(6) Upper MD	74 (10%)	71 (10%)	23 (10%)	
(7) Lower GR	56 (7%)	52 (7%)	14 (6%)	
(8) Upper GR	58 (8%)	55 (7%)	13 (6%)	
Baseline functional prognosis[b] [%] ($n^a = 749$)				
Pr(GOSE >1)	84.7 (63.5–94.9)	84.1 (62.1–94.7)	83.8 (66.9–94.0)	0.664
Pr(GOSE >3)	53.9 (29.9–76.0)	53.1 (29.2–75.0)	52.4 (33.9–71.1)	0.287
Pr(GOSE >4)	39.6 (20.6–59.6)	38.9 (19.8–58.3)	38.1 (22.6–54.6)	0.154
Pr(GOSE >5)	21.1 (10.2–36.8)	20.7 (10.0–36.0)	19.3 (10.5–30.1)	0.037
Pr(GOSE >6)	12.4 (5.9–20.8)	12.0 (5.8–19.9)	10.9 (5.8–17.2)	0.009
Pr(GOSE >7)	4.8 (2.2–9.2)	4.7 (2.2–9.1)	5.3 (2.2–8.5)	0.415
TIL_{max}	10 (6–14)	10 (6–14)	10 (6–14)	0.577
TIL_{median}	5 (3–10)	5 (3–10)	5 (4–10)	0.826
TIL_{24} scores				
Day 1 ($n^a = 852$)	7 (4–11)	7 (4–11)	7 (5–10)	0.134
Day 2 ($n^a = 839$)	6 (4–10)	6 (4–10)	6 (4–10)	0.860
Day 3 ($n^a = 819$)	6 (3–9)	6 (3–9)	6 (4–9)	0.926
Day 4 ($n^a = 787$)	6 (3–10)	6 (3–10)	5 (4–10)	0.372
Day 5 ($n^a = 761$)	5 (3–10)	5 (3–10)	5 (3–10)	0.941
Day 6 ($n^a = 733$)	5 (2–9)	5 (2.5–9)	5 (3–10)	0.337
Day 7 ($n^a = 709$)	5 (2–9)	4 (2–9)	5 (2–9)	0.425

[a]Limited sample size of non-missing values for characteristic.

[b]Ordinal functional outcome prognostic scores were calculated through tokenized embedding of all clinical information in the first 24 h of ICU stay, as described previously.[27]

[c]The p values, comparing patients in TIL-ICP$_{HR}$ sub-population to those not in TIL-ICP$_{HR}$ sub-population, are derived from with Welch's t-test for numeric variables and χ^2 contingency table test for categorical variables.

Data are median (interquartile range) for numeric characteristics and n (% of column group) for categorical characteristics, unless otherwise indicated. Units or numerical definitions of characteristics are provided in square brackets.

Baseline GCS, Glasgow Coma Scale at ICU admission, from 3 to 15; GOSE, Glasgow Outcome Scale-Extended; GR, good recovery; ICP, intracranial pressure; ICP$_{EH}$, end-hour ICP; ICP$_{HR}$, high-resolution ICP; Marshall CT, Marshall computerized tomography classification; MD, moderate disability; Pr(GOSE>•), ''probability of GOSE greater than • at 6 months post-injury'' as previously calculated from the first 24 h of admission[27]; SD, severe disability; TIL,Therapy Intensity Level scale; TIL_{24},TIL score of calendar day in ICU; TIL_{max}, maximum TIL_{24} over first week of ICU stay; TIL_{median}, median TIL_{24} over first week of ICU stay.

these patients from the others 81% (95% CI: 78-84%) of the time (Fig. 5A), and TIL_{median} did so 83% (95% CI: 80-86%) of the time (Fig. 5B). This performance of TIL was significantly greater than or similar to that of all alternative scales (Fig. 5A, 5B). Further, TIL_{median} had significantly greater discrimination performance than ICP_{max} (Fig. 5C) and ICP_{median} (Fig. 5D), respectively. The sensitivity and specificity of refractory intracranial hypertension detection at each threshold of TIL_{max}, TIL_{median}, $TIL^{(Basic)}{}_{max}$, and $TIL^{(Basic)}{}_{median}$ are listed in Supplementary Table S3 and visualized in Figure 5C and 5D. The thresholds which maximized the sum of sensitivity and specificity were $TIL_{max} \geq 14$ (sensitivity: 68% [95% CI: 62–74%], specificity: 79% [95% CI: 77-81%]) and $TIL_{median} \geq 7.5$ (sensitivity: 81% [95% CI: 77-87%], specificity: 72% [95% CI: 70-75%]; Table 3).

TIL component items

While there was wide variation in item combinations per TIL_{24} score (i.e., sum of median scores was often under diagonal line in Fig. 6A), the average order of therapeutic escalation was fairly consistent: position, sedation, CPP management, ventilatory management, neuromuscular blockade, hyperosmolar therapy, temperature control, and then surgery for refractory ICP. Surgical control of ICP occurred in over 50% of reported cases at each

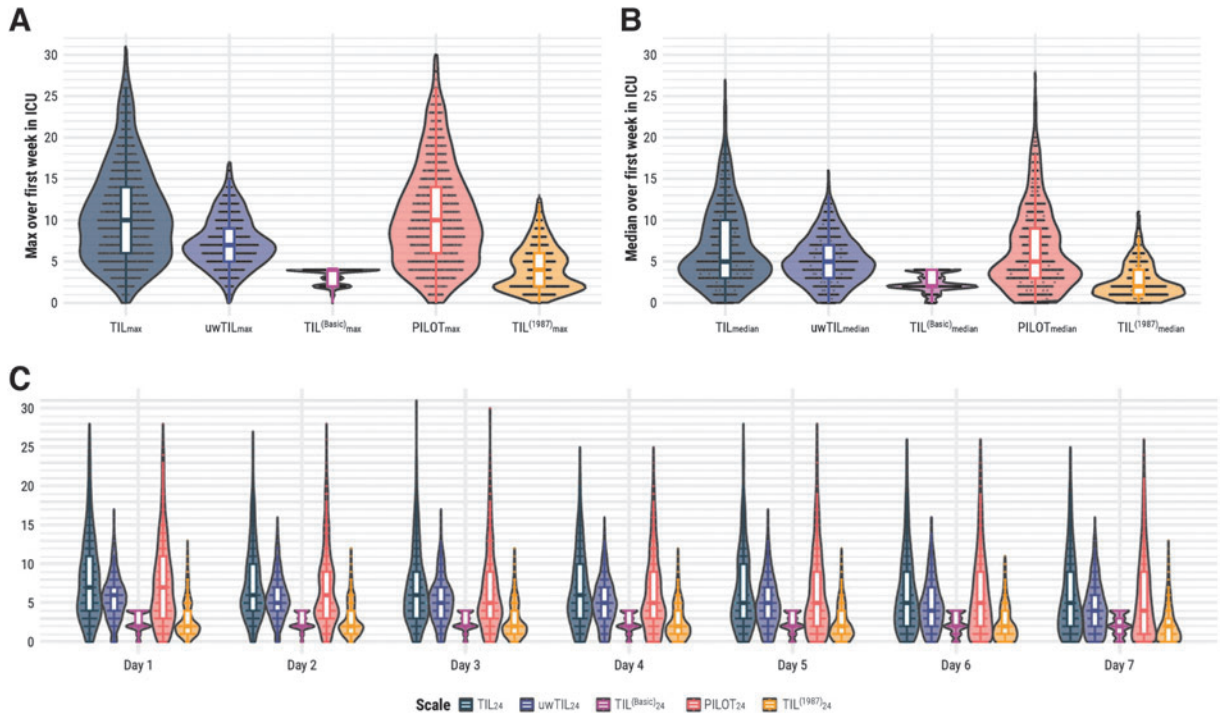
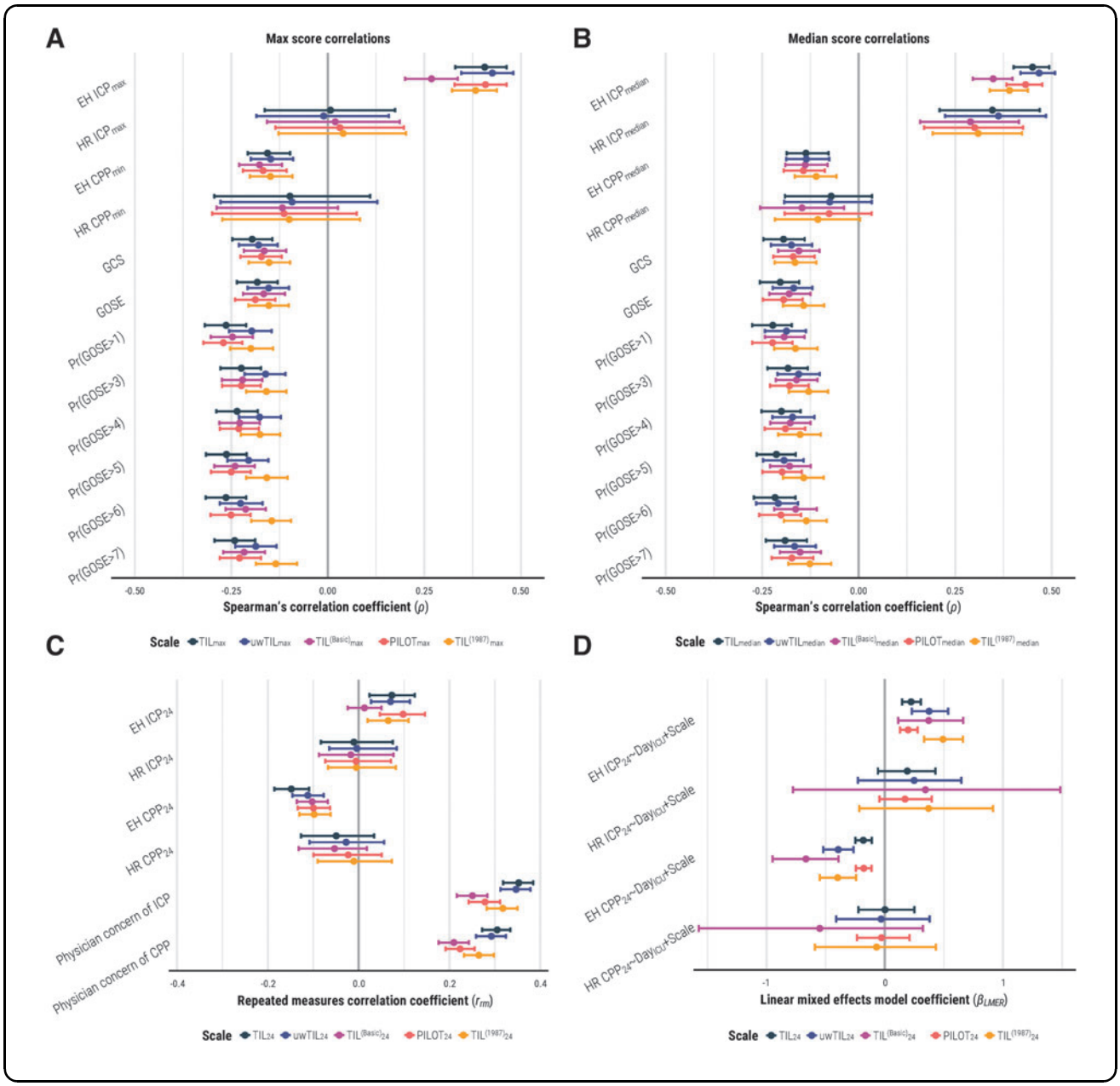


FIG. 2. Distributions of TIL and alternative scales. The numeric definition of each scale is listed in Table 1. (**A**) Distributions of maximum scores of TIL (i.e., TIL_{max}) and alternative scales (i.e., $uwTIL_{max}$, $TIL^{(Basic)}{}_{max}$, $PILOT_{max}$, and $TIL^{(1987)}{}_{max}$) over the first week of ICU stay. (**B**) Distribution of median scores of TIL (i.e., TIL_{median}) and alternative scales (i.e., $uwTIL_{median}$, $TIL^{(Basic)}{}_{median}$, $PILOT_{median}$, and $TIL^{(1987)}{}_{median}$) over the first week of ICU stay. (**C**) Distributions of daily scores of TIL (i.e., TIL_{24}) and alternative scales (i.e., $uwTIL_{24}$, $TIL^{(Basic)}{}_{24}$, $PILOT_{24}$, and $TIL^{(1987)}{}_{24}$) over the first week of ICU stay. ICU, intensive care unit; PILOT, Pediatric Intensity Level of Therapy scale[7]; TIL, Therapy Intensity Level scale[8,9]; $TIL^{(1987)}$, original Therapy Intensity Level scale published in 1987[6]; $TIL^{(Basic)}$, condensed TIL scale[8]; uwTIL, unweighted TIL scale in which sub-item scores are replaced by the ascending rank index within the item.

FIG. 3. Associations of TIL and alternative scales with other clinical measures. The numeric definition of each scale is listed in Table 1, and the calculation of daily (e.g., TIL_{24}), maximum (e.g., TIL_{max}), and median (e.g., TIL_{median}) scores are described in the "Methods" Section. The bars represent 95% confidence intervals derived from bootstrapping with 1,000 resamples of unique patients over 100 missing value imputations. (**A**) Spearman's correlation coefficients (ρ) between maximum scale scores over first week of ICU stay (i.e., TIL_{max}, $uwTIL_{max}$, $TIL^{(Basic)}{}_{max}$, $PILOT_{max}$, and $TIL^{(1987)}{}_{max}$) and other clinical measures. (**B**) Spearman's correlation coefficients (ρ) between median scale scores over first week of ICU stay (i.e., TIL_{median}, $uwTIL_{median}$, $TIL^{(Basic)}{}_{median}$, $PILOT_{median}$, and $TIL^{(1987)}{}_{median}$) and other clinical measures. (**C**) Repeated measures correlation coefficients (r_{rm}, from -1 to 1) are interpreted as the strength and direction of association between two variables after accounting for inter-patient variation. (**D**) Linear mixed effects model coefficients (β_{LMER}) are interpreted as the expected difference in dependent variable (e.g., EH ICP_{24}) per unit increase of daily scale score (e.g., TIL_{24}) after accounting for time since ICU admission (i.e., Day_{ICU}) and inter-patient variation. Day_{ICU}, variable representing day (from 1 to 7) of ICU stay; EH, end-hour; CPP, cerebral perfusion pressure; GCS, Glasgow Coma Scale at ICU admission; GOSE, Glasgow Outcome Scale–Extended at 6 months post-injury; HR, high-resolution; ICP, intracranial pressure; ICU, intensive care unit; PILOT, Pediatric Intensity Level of Therapy scale[7]; Pr(GOSE>•), "probability of GOSE greater than • at 6 months post-injury" as previously calculated from the first 24 h of admission[27]; TIL, Therapy Intensity Level scale[8,9]; $TIL^{(1987)}$, original Therapy Intensity Level scale published in 1987[6]; $TIL^{(Basic)}$, condensed TIL scale[8]; uwTIL, unweighted TIL scale in which sub-item scores are replaced by the ascending rank index within the item.

TIL_{24} above 18 (Fig. 6A), but the threshold which maximized the sum of sensitivity and specificity in detecting surgical ICP control was $TIL_{24} \geq 9$ (Table 3, performance at each threshold is listed in Supplementary Table S4).

The inter-item r_{rm} values of TIL_{24} (Supplementary Fig. S4) were mostly positive except for cerebrospinal fluid (CSF) drainage, which did not correlate significantly with most other items, and decompressive craniectomy, which did not correlate significantly with CSF, ventilatory, or temperature control. Consistent with Fig. 6A, this result suggested that CSF drainage and decompressive craniectomy were the most variably applied therapies across study ICUs. The Cronbach's alpha (α) value of TIL_{24} was, at best, 0.65 (95% CI: 0.62-0.68) and lower (albeit, not significantly) than that of $uwTIL_{24}$ at each day of ICU stay (Supplementary Fig. S5). However, since TIL is a formative scale (i.e., the construct is multidimensional and defined by the items), high inter-item correlation and α values are not necessary for item validation.[17] Among all TIL_{24} items, sedation was most strongly correlated with adjusted TIL_{24} scores and physician concerns of ICP (Fig. 6B). From $10 \leq TIL_{24} \leq 20$, a plateau effect of high-dose sedation combined with neuromuscular blockade was observed in most cases (Fig. 6A). When accounting for all other TIL_{24} subitems, time since ICU admission, as well as inter-patient variability, ventilation, mannitol administration, and hypertonic saline administration were most strongly associated with ICP_{24} and vasopressors were most strongly associated with CPP_{24} (Fig. 6C).



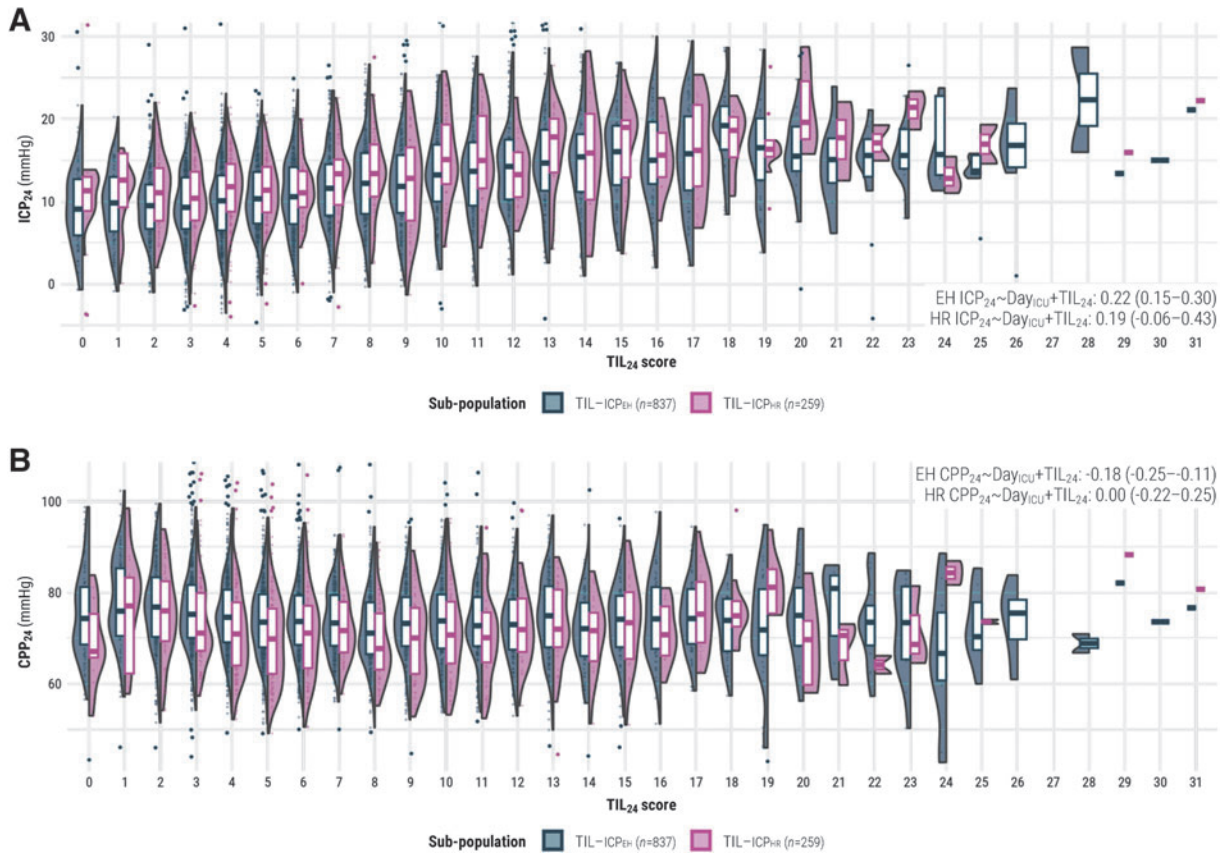


FIG. 4. Distributions of daily intracranial pressure and cerebral perfusion pressure means per daily TIL score. The values in each panel are the linear mixed effects model coefficients (β_{LMER}) of TIL_{24} with 95% confidence intervals derived from bootstrapping with 1000 resamples of unique patients over 100 missing value imputations. The width of violin plots is scaled for each population, but the width of the points inside them demonstrates relative frequency across the populations. The violin plots do not encompass outliers based on 1.5 times the interquartile range. (**A**) Distributions of ICP_{24} vs. TIL_{24} for both sub-populations. (**B**) Distributions of CPP_{24} vs. TIL_{24} for both sub-populations. CPP, cerebral perfusion pressure; CPP_{24}, mean CPP over calendar day; Day_{ICU}, variable representing day (from 1 to 7) of ICU stay; EH, end-hour; HR, high-resolution; ICP, intracranial pressure; ICP_{24}, mean ICP over calendar day; TIL, Therapy Intensity Level scale[8,9]; TIL_{24}, TIL score of calendar day; TIL-ICP_{EH}, end-hour ICP sub-population; TIL-ICP_{HR}, high-resolution ICP sub-population.

$TIL^{(Basic)}$

Based on the median $TIL^{(Basic)}{}_{24}$ score at each TIL_{24} score (Fig. 7A), we derived the ranges for mapping TIL_{24} onto $TIL^{(Basic)}{}_{24}$ in Table 3. There is, however, considerable overlap of TIL_{24} scores across $TIL^{(Basic)}{}_{24}$ scores (Fig. 7B), particularly in the range of $6 \leq TIL_{24} \leq 10$. $TIL^{(Basic)}{}_{24} = 3$ was not the most represented score at any TIL_{24} score (Fig. 7A). $TIL^{(Basic)}{}_{24}$ covered up to 33% (95% CI: 31-34%) of the information (i.e., entropy) in TIL_{24}, and $TIL^{(Basic)}{}_{median}$ covered up to 28% (95% CI: 27-30%) of the information in TIL_{median} (Fig. 7C). $TIL^{(Basic)}{}_{max}$ only covered 17% (95% CI: 16-18%) of the information in TIL_{max} (Fig. 7C).

Discussion

In this work, we performed a large-scale ($n = 873$), multicenter (52 ICUs, 19 countries), and prospective validation study of TIL and $TIL^{(Basic)}$ against alternative scales. Our results support the validity of TIL as a metric for scoring ICP-directed therapeutic intensity. The dataset we used, as part of the CENTER-TBI study, not only reflects the modern variation in ICP-directed therapeutic intensity (Fig. 2 and Fig. 6A) but also illustrates the practical feasibility of daily TIL assessment: of 885 eligible patients, 873 (99%) had daily TIL scores (Fig. 1) with less than 2.4% daily missingness (Supplementary Fig. S2).

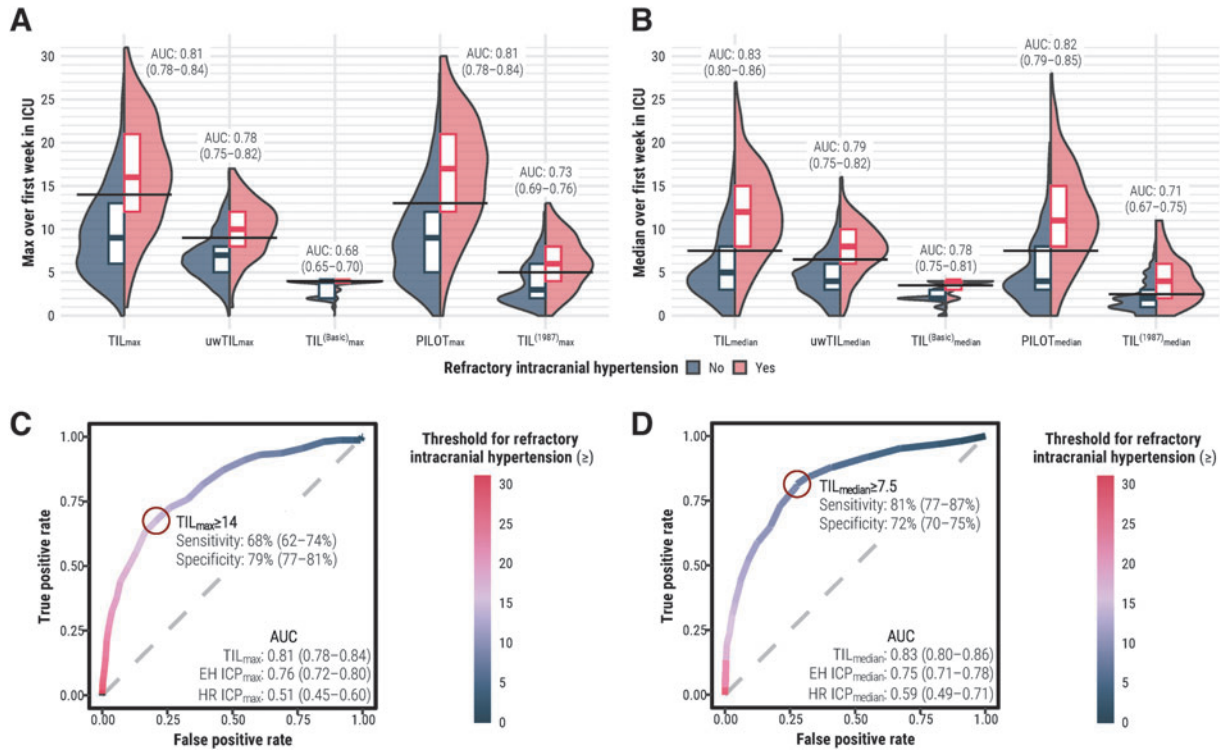


FIG. 5. Discrimination of refractory intracranial hypertension status by TIL and alternative scale summary scores. The 95% confidence intervals of AUC were derived from bootstrapping with 1,000 resamples of unique patients over 100 missing value imputations. (**A**) Distributions of maximum scores of TIL (i.e., TIL_{max}) and alternative scales (i.e., $uwTIL_{max}$, $TIL^{(Basic)}{}_{max}$, $PILOT_{max}$, and $TIL^{(1987)}{}_{max}$) stratified by refractory intracranial hypertension status. The horizontal black line segments represent the thresholds which maximized the sum of sensitivity and specificity for each scale. (**B**) Distributions of median scores of TIL (i.e., TIL_{median}) and alternative scales (i.e., $uwTIL_{median}$, $TIL^{(Basic)}{}_{median}$, $PILOT_{median}$, and $TIL^{(1987)}{}_{median}$) stratified by refractory intracranial hypertension status. The horizontal black line segments represent the thresholds which maximized the sum of sensitivity and specificity for each scale. (**C**) Receiver operating characteristic curve of refractory intracranial hypertension detection with TIL_{max}. The threshold which maximized the sum of sensitivity and specificity is highlighted with the dark red circle. (**D**) Receiver operating characteristic curve of refractory intracranial hypertension detection with TIL_{median}. The threshold which maximized the sum of sensitivity and specificity is highlighted with the dark red circle. AUC, area under the receiver operating characteristic curve, EH, end-hour; HR, high-resolution; ICP, intracranial pressure; ICP_{max}, maximum calendar day mean of ICP over first week of ICU stay; ICP_{median}, median calendar day mean of ICP over first week of ICU stay; ICU, intensive care unit; PILOT, Pediatric Intensity Level of Therapy scale[7]; TIL, Therapy Intensity Level scale[8,9]; $TIL^{(1987)}$, original Therapy Intensity Level scale published in 1987[6]; $TIL^{(Basic)}$, condensed TIL scale[8]; uwTIL, unweighted TIL scale in which sub-item scores are replaced by the ascending rank index within the item.

We scrutinized and validated the use of TIL as a metric for scoring ICP-directed therapeutic intensity and for marking pathophysiological severity. The statistical construct and criterion validity measures of TIL were significantly greater or similar to those of alternative scales (Fig. 3 and Fig. 5), and TIL integrated the widest range of modern ICP treatments (Table 1). Summarized TIL scores outperformed summarized ICP values in detecting refractory intracranial hypertension. Our analysis yielded empirical ranges for interpreting TIL in terms of refractory intracranial hypertension, surgical intervention, and the condensed, $TIL^{(Basic)}$ scores (Table 3). On a component level (Fig. 6A), TIL_{24} reflected a pattern of treatment intensity escalation consistent with clinical algorithms[2,3,5] as well as a wide variation in treatment combinations, particularly in the use of CSF drainage

Table 3. Optimized Ranges for TIL Categorization

Category	Derived ranges	Performance (95% confidence intervals)			Case counts[c]		Previously proposed ranges[d]
		Sensitivity	Specificity	Accuracy	No	Yes	
Refractory intracranial hypertension[a]	$TIL_{max} \geq 14$	68% (62–74%)	79% (77–81%)	77% (75–79%)	707	157	$TIL_{max} \geq 11$
	$TIL_{median} \geq 7.5$	81% (77–87%)	72% (70–75%)	74% (72–76%)			–
Day of surgical ICP control[b]	$TIL_{24} \geq 9$	87% (83–91%)	74% (72–76%)	76% (74–77%)	4916	585	–
$TIL^{(Basic)}{}_{24}$				72% (70–73%)			
(1) Basic ICU care	$1 \leq TIL_{24} \leq 2$				4932	568	$1 \leq TIL_{24} \leq 3$
(2) Mild	$3 \leq TIL_{24} \leq 6$				3294	2206	$4 \leq TIL_{24} \leq 7$
(3) Moderate	$7 \leq TIL_{24} \leq 8$				4709	791	$8 \leq TIL_{24} \leq 10$
(4) Extreme	$TIL_{24} \geq 9$				3919	1581	$TIL_{24} \geq 11$

The numeric definition of each scale is listed in Table 1, and the calculation of daily (e.g., TIL_{24}), maximum (e.g., TIL_{max}), and median (e.g., TIL_{median}) scores is described in the Methods. The 95% confidence intervals of performance metrics were derived from bootstrapping with 1000 resamples of unique patients over 100 missing value imputations.

[a]Refractory intracranial hypertension was defined as recurrent, sustained (i.e., of at least 10 min) increases of ICP above 20 mm Hg despite medical ICP management during ICU stay. This information was recorded by attending physicians in patient discharge summaries.

[b]If a decompressive craniectomy was performed as a last resort for refractory intracranial hypertension, each of the days following the operation were also considered days of surgical ICP control.

[c]For refractory intracranial hypertension, case counts represent the number of patients (with non-missing values) without (i.e., No) and with (i.e., Yes) refractory intracranial hypertension. For day of surgical ICP control and $TIL^{(Basic)}{}_{24}$, case counts represent the number of non-missing TIL assessments not in (i.e., No) and in (i.e., Yes) the given category.

[d]Thresholds were previously proposed by the interagency panel which developed TIL based on expert opinion.[8]

ICP, intracranial pressure; ICU, intensive care unit; TIL, Therapy Intensity Level scale[8,9]; $TIL^{(Basic)}$, condensed TIL scale.[8]

and decompressive craniectomy. This finding is consistent with a previous CENTER-TBI study—which revealed inter-center variation in TIL treatment selection and time to administration[12]—and encourages an investigation of differences in TIL and long-term outcome between centers with known differences in ICP management strategies. In summary, our results support the use of TIL as an intermediate outcome for treatment effect, as done in previous studies.[33-35]

Due to a strong ceiling effect (Fig. 2A and Fig. 5A), $TIL^{(Basic)}$ should not be used instead of TIL for rating maximum treatment intensity. $TIL^{(Basic)}{}_{24}$ and TIL_{median} covered up to 33% of the information in TIL_{24} (Fig. 7C), but the $TIL^{(Basic)}{}_{24}$ associations with physician concerns of ICP were significantly worse than those of TIL_{24} (Fig. 3C). TIL should always be preferred to $TIL^{(Basic)}$, but we believe daily or median $TIL^{(Basic)}$ can be a suitable alternative when daily or median TIL assessment is infeasible.

Moreover, we evaluated TIL with both end-hour (ICP_{EH}) and high-resolution (ICP_{HR}) ICP values. ICP_{HR}, if available, should be considered the gold standard in terms of precision and granularity of the information provided, and neuromonitoring-related results from the ICP_{HR} population should generally take precedence.[14] However, 67% of expected ICP_{HR} values were missing on Day 1 of ICU stay (Supplementary Fig. S2), likely due to the time required to arrange high-resolution data collection. Consequently, estimates of high-resolution ICP_{max} were significantly affected by missing value imputation and became imprecise at our sample size (Fig. 3A). In these cases, results from the ICP_{EH} population served as a valuable reference on a substantially larger sample size (Table 2) since ICP_{EH} and CPP_{EH} have been shown to be fair end-hour representations of ICP_{HR} and CPP_{HR}, respectively, in CENTER-TBI.[14] The considerable overlap of ICP_{24} values across TIL_{24} scores (both at low and high levels of ICP, Fig. 4A) and the insignificant-to-weak within-individual association between ICP_{24} and TIL_{24} (Fig. 3C–D) highlight the need to account for therapeutic intensity when interpreting ICP. Additionally, the higher median ICP_{24} values for $TIL_{24} \geq 8$ (Fig. 4A) may suggest that clinicians accept a slightly higher ICP when balancing the risks of elevating therapeutic intensity against those of intracranial hypertension.

We see three main opportunities to improve TIL. First, the item scores of TIL and its predecessors (i.e., PILOT and $TIL^{(1987)}$) were not derived empirically. Data-driven techniques, such as confirmatory factor analysis,[28] can be used to derive scoring configurations, which optimize a defined objective (e.g., maximal separation of patients). However, data-driven scores do not necessarily reflect the intended construct (i.e., treatment risk and complexity),[36] and, in general, item scoring does not have an appreciable impact on overall scale performance.[28] Second, the items of TIL must evolve as therapeutic approaches to ICP management evolve. TIL discriminated refractory intracranial hypertension status significantly better than $TIL^{(1987)}$ (Fig. 5A, 5B) because TIL updated $TIL^{(1987)}$ with six additional items (Table 1). We recommend updating and re-evaluating TIL each time ICP-treatment modalities or their perceived risks change. Finally, the development of TIL was largely informed by the perspective of ICU practices in high-income countries.[8] Likewise, this assessment was performed in a cohort of patients across Europe and Israel. Especially given the disproportionately higher burden of TBI in

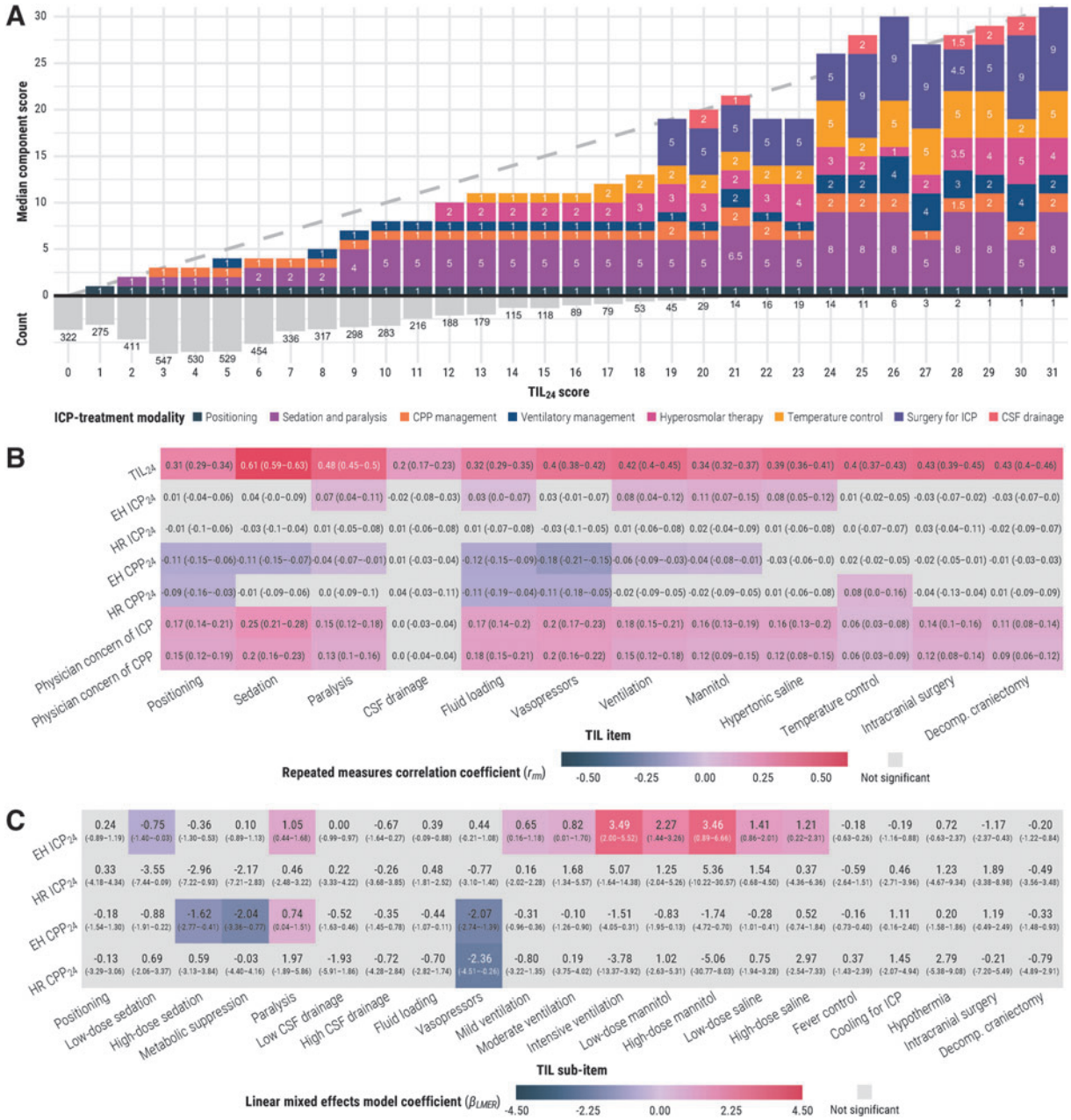


FIG. 6. Association of TIL component items with TIL_{24} and other study measures. The 95% confidence intervals of r_{rm} and β_{LMER} values were derived from bootstrapping with 1000 resamples of unique patients over 100 missing value imputations. (**A**) Median component score of each ICP-treatment modality (Table 1) per each TIL_{24} score. The histogram under the *x*-axis represents the relative frequency and count of each TIL_{24} score in the population, and diagonal dashed line represents the TIL_{24} score on both axes. If the sum of median item scores does not equal the corresponding TIL_{24} score, this can be interpreted as high variability in the combination of simultaneously applied therapies at that TIL_{24} score. (**B**) The repeated measures correlation coefficients (r_{rm}, from -1 to 1) are interpreted as the strength and direction of association between two variables after accounting for inter-patient variation. The component score of each item (Table 1, *x*-axis) was subtracted from the TIL_{24} score (top row on *y*-axis) before calculating their r_{rm} values. (**C**) Linear mixed effects model coefficients (β_{LMER}) are interpreted as the expected difference in the dependent variable (*y*-axis) associated with the given TIL_{24} sub-item treatment (Table 1) after accounting for all other TIL_{24} sub-items, time since ICU admission, and inter-patient variation. CPP, cerebral perfusion pressure; CPP_{24}, mean CPP over calendar day; CSF, cerebrospinal fluid; EH, end-hour; HR, high-resolution; ICP, intracranial pressure; ICP_{24}, mean ICP over calendar day; ICU, intensive care unit; TIL, Therapy Intensity Level scale[8,9]; TIL_{24}, TIL score of calendar day.

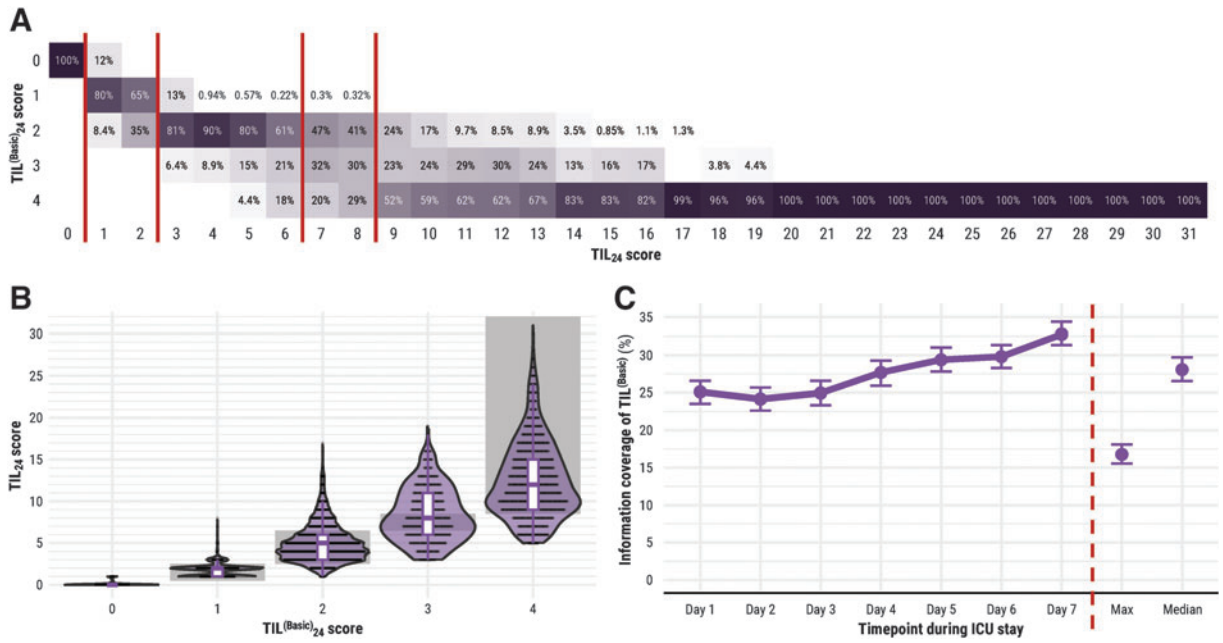


FIG. 7. Relationship between TIL and $TIL^{(Basic)}$. The numeric definition of each scale is listed in Table 1, and the calculation of daily (e.g., TIL_{24}), maximum (e.g., TIL_{max}), and median (e.g., TIL_{median}) scores are described in the "Methods" section. The 95% confidence intervals of information coverage were derived from bootstrapping with 1000 resamples of unique patients over 100 missing value imputations. (**A**) Distribution of corresponding $TIL^{(Basic)}_{24}$ scores per each TIL_{24} score. The values in each cell represent the percent of assessments at a given TIL_{24} score (i.e., column) corresponding to a $TIL^{(Basic)}_{24}$ score (i.e., row). The vertical, dark red lines represent cut-offs across which the median corresponding $TIL^{(Basic)}_{24}$ score per TIL_{24} score changes. (**B**) Distribution of corresponding TIL_{24} scores per each $TIL^{(Basic)}_{24}$ score. The width of violin plots is scaled for each $TIL^{(Basic)}_{24}$ score, but the width of the points inside them demonstrates relative frequency across the $TIL^{(Basic)}_{24}$ scores. The grey, shaded zones represent the range of TIL_{24} scores with corresponding median $TIL^{(Basic)}_{24}$ scores on the *x*-axis, as determined in panel (A). (**C**) The information of TIL_{24}, TIL_{max}, and TIL_{median} covered by $TIL^{(Basic)}_{24}$, $TIL^{(Basic)}_{max}$, and $TIL^{(Basic)}_{median}$, respectively. Information coverage is defined as the mutual information of TIL_{24} and $TIL^{(Basic)}_{24}$ (or TIL_{max} and $TIL^{(Basic)}_{max}$ or TIL_{median} and $TIL^{(Basic)}_{median}$) divided by the entropy of TIL_{24} (or TIL_{max} or TIL_{median}). AUC, area under the receiver operating characteristic curve; ICU, intensive care unit; TIL, Therapy Intensity Level scale[8,9]; $TIL^{(Basic)}$, condensed TIL scale.[8]

low- and middle-income countries,[37] it is imperative to test and, if necessary, adapt TIL to a more inclusive, global population of TBI.

By design, TIL does not encompass all facets of modern intensive care for TBI patients. Brain tissue oxygen tension ($PbtO_2$),[38] cerebral microdialysis,[39] and brain temperature[40] have emerged as multi-modal neuromonitoring targets that may affect ICU management in addition to ICP or CPP. Therefore, TIL should be interpreted not as general treatment intensity but rather as the intensity of ICP-directed therapy specifically. We encourage the development and validation of clinical scales assessing the intensity of TBI treatments directed at other physiological targets. Since treatments for other targets often overlap with those for ICP or CPP (e.g., vasopressors target both $PbtO_2$ and CPP),[2] we also promote a consolidation of all TBI treatments in an overall therapeutic intensity scale which considers the effect of each treatment on multiple physiological targets.

We recognize several limitations of our analysis. Whilst numerous investigators assessed TIL across the study ICUs, each TIL score was only assessed once. Therefore, we could not evaluate the inter-rater reliability of TIL. Similarly, data needed to calculate the full TIL score were only recorded once a day, so we could not determine if a daily assessment frequency was sufficient. Since the prior TIL validation study reported a high inter-rater reliability and recommended a daily assessment frequency,[9] we assumed both to be true. The results from the Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp) trial[41]—published amidst

CENTER-TBI patient recruitment in 2016—have likely changed the global frequency and perceived intensity of decompressive craniectomy for TBI. Therefore, we recognize the potentially confounding effect of the trial results on treatment decision making for some patients in the CENTER-TBI population and encourage a potential reappraisal of the therapeutic intensity of decompressive craniectomy through expert discussion and statistical validation. The physician impressions (i.e., physician concerns of ICP and CPP and refractory intracranial hypertension status) were subjective, and we did not have enough information to account for inter-rater variability. Therefore, these scores and labels should be considered unrefined. Finally, because of limited dosage data for numerical treatments (i.e., CSF drainage, ventilation, hyperosmolar therapy, and temperature control), we did not test alternative sub-item categorizations.

Conclusion

TIL is a valid, generalizable measurement of ICP management amongst neuro-monitored TBI patients in the ICU. On all validation metrics, TIL performs at least as well as its alternatives and considers the widest range of modern treatment strategies. TIL's component scores over increasing TIL reflect a clinically credible order of treatment escalation, from head positioning to ICP-directed surgery. $TIL^{(Basic)}$ is not suitable for evaluating maximum treatment intensity, but daily $TIL^{(Basic)}$ and median $TIL^{(Basic)}$ can cover up to a third of the information in TIL. In the setting of clinical ICP management, TIL is a more sensitive marker of pathophysiological severity than ICP and can be considered an intermediate outcome after TBI.

Transparency, Rigor, and Reproducibility Summary

The CENTER-TBI study was pre-registered at clinicaltrials.gov (NCT02210221, https://clinicaltrials.gov/ct2/show/NCT02210221). The analysis plan was registered after beginning data collection but before data analysis at https://www.center-tbi.eu/data/approved-proposals (#491), and the lead author with primary responsibility for the analysis certifies that the analysis plan was prespecified. A sample size of 903 patients was planned based on availability of critically ill, ICP-monitored, adult TBI patients recruited for CENTER-TBI. Actual sample size was 873, as 18 patients had a documented decision to WLST on the first day of ICU stay and 12 additional patients did not have daily TIL scores assessed. A patient inclusion diagram is provided (Fig. 1). TIL scoring and clinical data entry was performed by investigators who were aware of relevant characteristics of the participants. Participants were recruited between December 19, 2014, and December 17, 2017, and data (including follow-up results) were collected until March 31, 2021. High-resolution waveforms were stored directly from bedside monitoring software, as described in the ''Methods'' section. Variability amongst different TIL assessors is not expected to be significant based on the established high inter-rater reliability of TIL.[9] All equipment and software used to perform imaging and preprocessing are widely available from commercial sources or open source repositories. The clinimetric validation procedure and the primary clinical metric (TIL) are established standards in the field, based on previously published results[9,28] and this study. The assumption of bootstrapping-derived confidence intervals is that the sample is representative of the population. This study is, itself, an external validation, and internal replication by the study group was performed. Individual participant data are available online, conditional to approved online study proposal, with no end date at https://www.center-tbi.eu/data. Signed confirmation of a data access agreement is required, and all access must comply with regulatory restrictions imposed on the original study. All analytic code used to perform the statistical analyses are publicly available online at https://github.com/sbhattacharyay/CENTER-TBI_TIL. This paper will be published under a Creative Commons Open Access license, and upon publication, will be freely available at https://www.liebertpub.com/loi/neu.

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Authors' Contributions

S.B. co-conceptualized the aims, developed the methodology and design, curated, analysed, and visualized the data, acquired funding, and wrote the manuscript. E.B. curated and analysed data, acquired funding, and reviewed the manuscript. P.Z. and L.W. curated data, aided in the development of methodology, and reviewed the manuscript. EWS and DWN curated data, acquired funding, advised statistical analysis, and reviewed the manuscript. A.I.R.M. and D.K.M. curated data, acquired funding, co-conceptualized the aims, co-developed the methodology, and reviewed the manuscript. A.E. served as principal investigator, curated data, conceptualized the aims, co-developed the methodology, and reviewed the manuscript. All authors read and approved the final manuscript.

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Supplementary Material

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