Photo credit: Emilio Floris

Predicting Clinical Outcomes in Visceral Leishmaniasis

James Wilson

Infectious Diseases Data Observatory

Oxford Centre for Tropical Medicine and Global Health

University of Oxford

Conflict of Interest:
The author has declared no conflict of interest.

Clinical case

- 30-year-old, Northern Ethiopia
- 4 weeks intermittent fever, weight loss
- Febrile, tachycardic, splenomegaly
- Malaria negative, HIV negative
- rK39 rapid diagnostic test positive
- Haemoglobin 6.5 g/dL

Photo credit: DNDi. (Otieno) 2019

What do you do?

What is a prediction model?

> "... a **mathematical equation** that relates **multiple** predictors for a particular individual to the probability of or risk for the presence (diagnosis) or future occurrence (prognosis) of a particular outcome" [TRIPOD, 2015]

Why?

- Risk stratification
- Guideline development
- Research

OPEN ACCESS Freely available online

PLOS NEGLECTED TROPICAL DISEASES

Sodium Stibogluconate (SSG) & Paromomycin Combination Compared to SSG for Visceral Leishmaniasis in East Africa: A Randomised Controlled Trial

Am. J. Trop. Med. Hyg., 101(4), 2019, pp. 795–798
doi:10.4269/ajtmh.19-0179

Effectiveness of Single-Dose Liposomal Amphotericin B in Visceral Leishmaniasis in Bihar

Shyam Sundar,[1]* Anup Singh,[1] Neha Agrawal,[2] and Jaya Chakravarty[1]
[1]*Institute of Medical Sciences, Banaras Hindu University, Varanasi, India;* [2]*Temple University, Philadelphia, Pennsylvania*

36 clinical trials
> 9,300 patients

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Efficacy and safety of available treatments for visceral leishmaniasis in Brazil: A multicenter, randomized, open label trial

OPEN ACCESS Freely available online

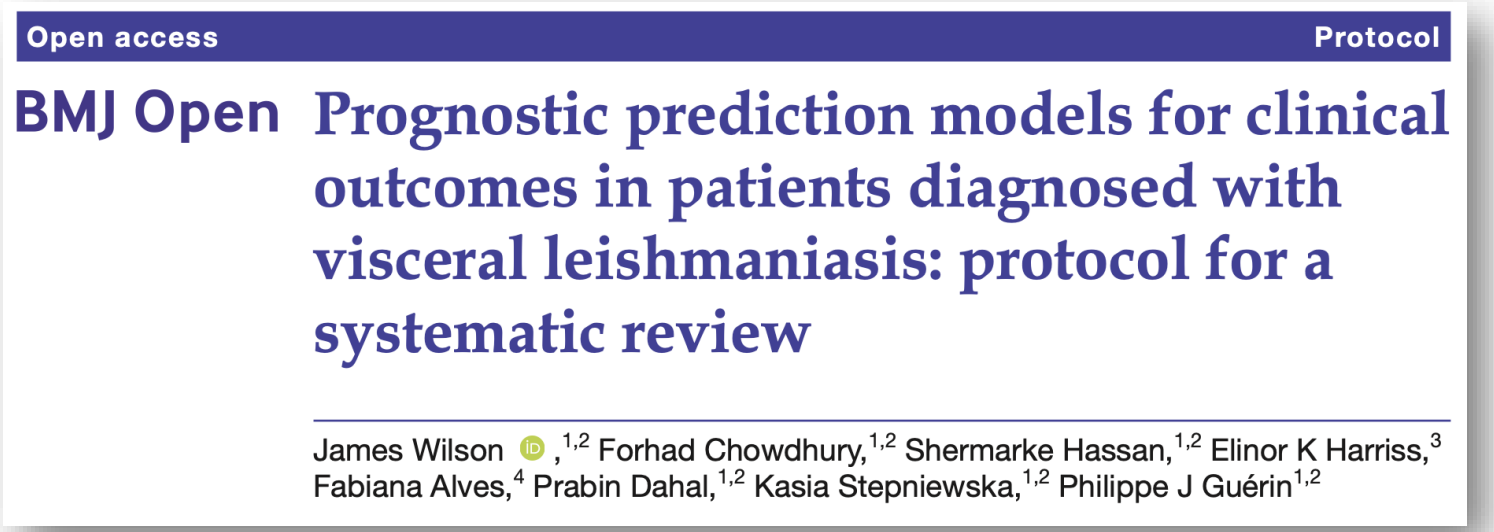
PLOS | NEGLECTED TROPICAL DISEASES

Efficacy and Safety of Amphotericin B Emulsion versus Liposomal Formulation in Indian Patients with Visceral Leishmaniasis: A Randomized, Open-Label Study

MEDECINS SANS FRONTIERES

SCIENTIFIC DAYS

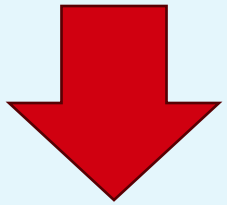
Identifying gaps in evidence



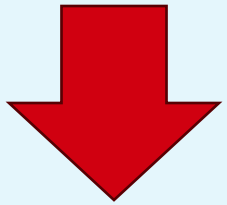
- **Aim**
  - To *identify*, *appraise* and *compare* all models predicting VL outcomes
- **Methods**
  - No restriction on language or date of publication
  - Including all models predicting any future clinical outcome
  - Excluding: abstracts, educational works, guidelines

How do you assess a prediction model?

Population used for testing model?



Applicability



Performance

Model result

- 20% mortality risk over 1 month

Discrimination

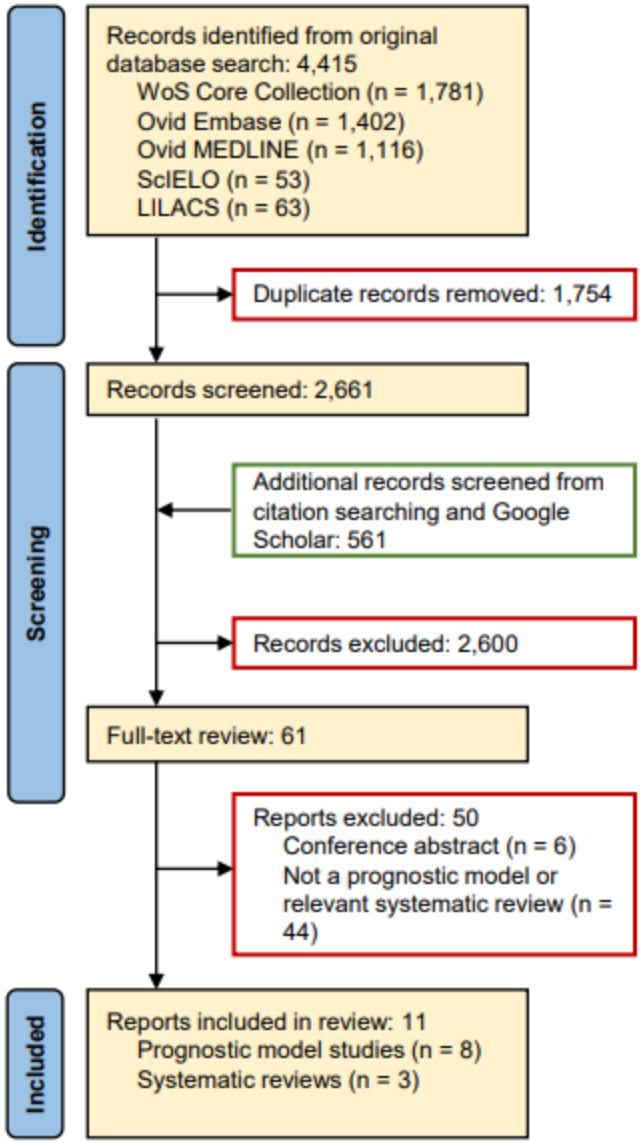
- Ability to discriminate between patients who die and patients who survive

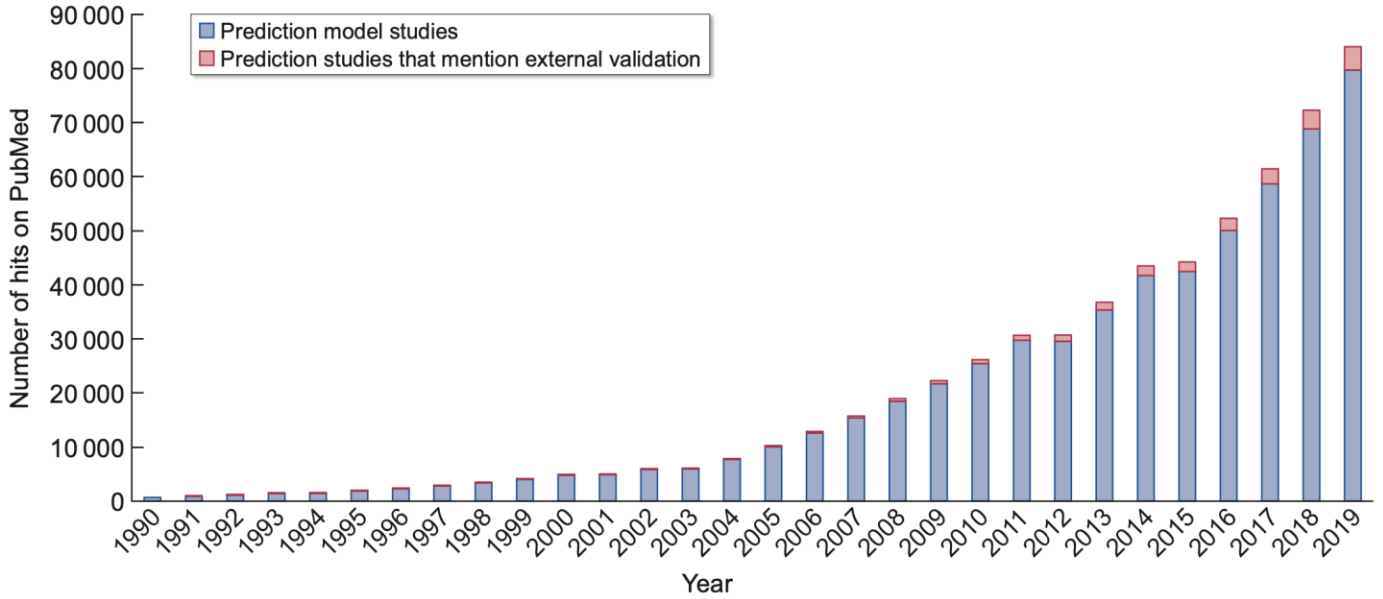
Calibration

- How *trustworthy* is the estimate of 20% mortality?

Results

- 8 studies identified
  - 12 model developments
  - 19 external validations
- Outcome: **always mortality**
- Location
  - **East Africa**: 2 studies reporting 3 models
  - **Brazil**: 6 studies reporting 9 models
- Risk of bias: **high** for all models
  - Small sample sizes
  - Risk scores not reproducible
- All models reported discrimination
- No models reported calibration





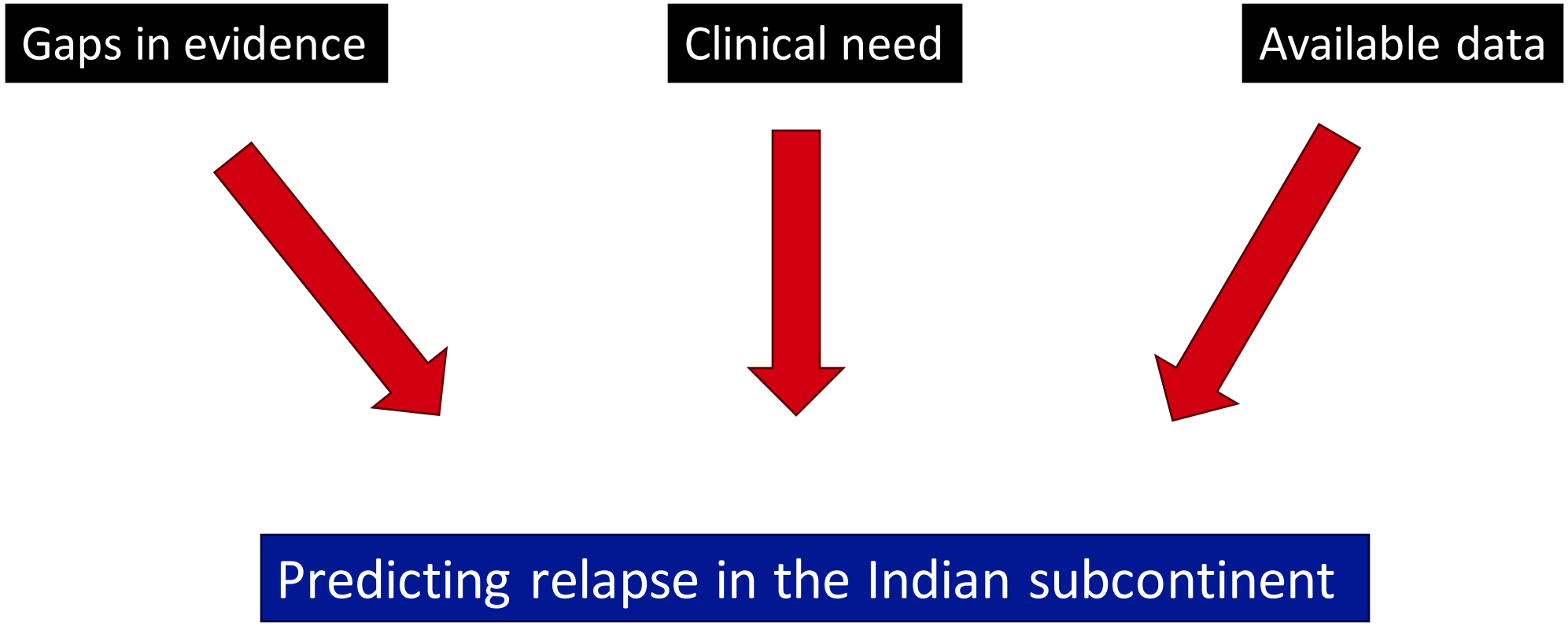
Ramspek CL, Jager KJ, Dekker FW, Zoccali C, van Diepen M. External validation of prognostic models: what, why, how, when and where? Clin Kidney J. 2020 Nov 24;14(1):49-58

Disease	# of models	Reference
COVID-19	606	Wynants, 2022
COPD prognostic	408	Bellou, 2019
Cardiovascular disease	363	Damen, 2016
Obstetrics prognosis	263	Kleinrouweler, 2016
Pulmonary TB prognosis	37	Peetluk, 2021
Malaria prognosis	27	Njim, 2019
Bacterial meningitis diagnosis	17	van Zeggeren, 2022

MEDECINS SANS FRONTIERES

SCIENTIFIC DAYS

What's next?


Gaps in evidence
Clinical need
Available data
Predicting relapse in the Indian subcontinent

Summary

- Prediction models are important!
- IDDO VL data repository
- Systematic review of VL prediction models
- High risk of bias limits model interpretation
- Currently developing a prognostic model for VL relapse in the Indian Subcontinent

Dr D. Pandey/WHO India. Indoor residual spraying for vector control in a high kala-azar endemic village.

Thank you!

- All our collaborators and colleagues from around the world!

IDDO
INFECTIOUS DISEASES DATA OBSERVATORY

- Data curation team
- Prof Philippe Guérin
- Dr Prabin Dahal
- Prof Ahmed Musa

KALA - AZAR MEDICAL RESEARCH CENTRE
Sitaram Memorial Trust

icmr INDIAN COUNCIL OF MEDICAL RESEARCH | RMRIMS RAJENDRA MEMORIAL RESEARCH INSTITUTE OF MEDICAL SCIENCE

DNDi

INSTITUTE OF TROPICAL MEDICINE ANTWERP

MEDECINS SANS FRONTIERES

SCIENTIFIC DAYS

medRxiv

THE PREPRINT SERVER FOR HEALTH SCIENCES

Cold Spring Harbor Laboratory BMJ Yale

Follow this preprint

Prognostic Models Predicting Clinical Outcomes in Patients Diagnosed with Visceral Leishmaniasis: A Systematic Review

James P Wilson, Forhad Chowdhury, Shermarke Hassan, Eli Harriss, Fabiana Alves, Ahmed Musa, Prabin Dahal, Kasia Stepniewska, Philippe J Guérin

doi: https://doi.org/10.1101/2024.03.20.24304622

Extra slides

Age group 19 years and above: Adults

BMI		Age		Hb	
Cut-off	*Score*	*Cut-off*	*Score*	*Cut-off*	*Score*
over 16	0	below 30 yrs	0	over 8 g/dl	0
14 - 16	1	30 – 39 yrs	1	6 – 8 g/dl	1

Age group below 19 years: Children & Adolescents

W/H Z-score		Age		Hb	
Cut-off	*Score*	*Cut-off*	*Score*	*Cut-off*	*Score*
-2 and above	0	above 5 yrs	0	over 8 g/dl	0
<-2	1	2 – 5 yrs	1	6 – 8 g/dl	1
<-3	2	1 – 2 yrs	3	4 – 6 g/dl	2
<-4	3	below 1 yr	4	below 4 g/dl	4
13 – 13.9	2	40 – 44 yrs	3	4 – 6 g/dl	2
12 – 12.9	3	45 yrs and above	5	below 4 g/dl	4
below 12	4				

Level of weakness

State of collapse = score 5

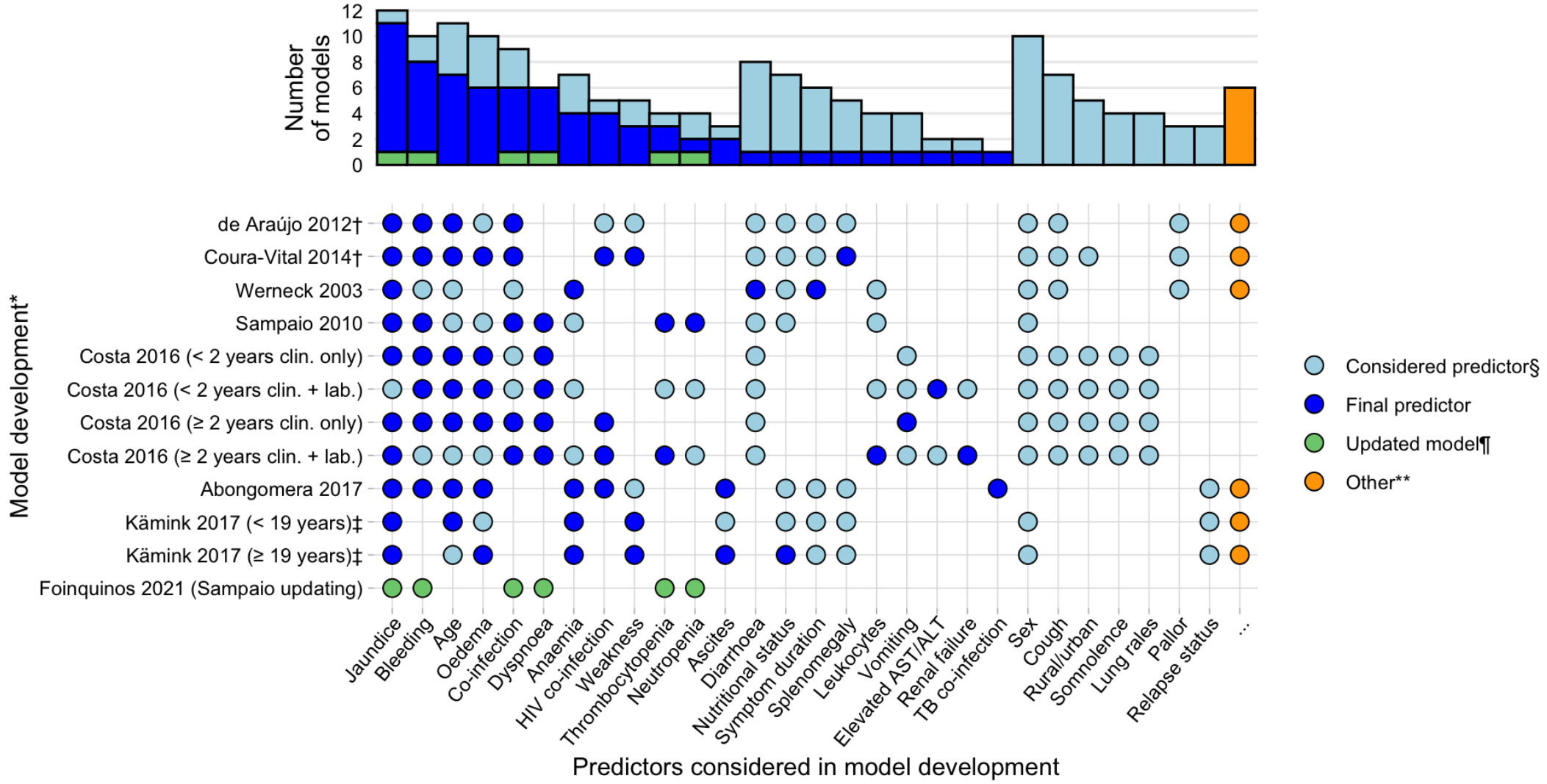
- Definition of collapse in adults/older children: unable to sit up unaided AND cannot drink unaided
- Definition of collapse in babies: floppy when held in arms AND unable to feed unaided

Severely weak = score 3

- Definition of severe weakness in adults/older children: cannot walk 5 m without assistance
- Definition of severe weakness in babies: unable to sit upright unaided

Other types of weakness = score 0

Systematic review results



Study	Model described	Data Source	Location Years	Age criteria Diagnostic criteria	Age Spread	% Male	% HIV positive	Events* Sample size (%)	Predictors† Final, Candidate	EPP
Outcome: Registry-reported mortality										
de Araújo 2012 (33)	-	Registry	**Brazil (Belo Horizonte)** 2007-09	- susp. *and* conf.	-	-	-	**49** 376 (13.0%)	**4**, 48	1.0
Coura-Vital 2014 (20)	-	Registry	**Brazil (Nationwide)** 2007-11	- conf.	¶	61.7%	7.0%	**770** 12,333 (6.2%)	**12**, (29)	(26.6)
Outcome: In-hospital mortality										
Werneck 2003 (21)	-	Case-control	**Brazil (Teresina)** - (< 2003)	- lab.	**Mean: 14.2yrs** -	68.9%	-	**12** 90 (13.3%)	**4**, (15)	(0.8)
Sampaio 2010 (34)	-	Retrospective	**Brazil (Recife)** 1996-2006	**< 15 years** lab. *or* clin.	**Median: 3.2yrs** Range: 4m-13.7yrs	50.4%	-	**57** 546 (10.4%)	**6**, (15)	(3.8)
Costa 2016 (14)	< 2 years, clin. only	Prospective	**Brazil (Teresina)** 2005-08	**< 2 years** lab. *and* clin.	-	-	-	**-§** 314 (-%)	**6**, (25)	(0.9)
	< 2 years, clin. + lab.	Prospective	**Brazil (Teresina)** 2005-08	**< 2 years** lab. *and* clin.	-	-	-	**-§** 291 (-%)	**6**, (31)	(0.7)
	≥ 2 years, clin. only	Prospective	**Brazil (Teresina)** 2005-08	**≥ 2 years** lab. *and* clin.	-	-	-	**-§** 569 (-%)	**9**, (27)	(1.6)
	≥ 2 years, clin. + lab.	Prospective	**Brazil (Teresina)** 2005-08	**≥ 2 years** lab. *and* clin.	-	-	-	**-§** 538 (-%)	**9**, (33)	(1.2)
Abongomera 2017 (13)	-	Retrospective	**Ethiopia (Abdurafi)** 2008-13	- lab. *and* clin.	**Median: 23yrs** IQR: 20-28yrs	95.9%	19.3%	**99** 1,686 (5.9%)	**8**, 16	6.2
Kämink 2017 (35)	< 19 years	Retrospective	**South Sudan (Lankien)** 2013-15	**< 19 years** lab. *and* clin.	¶	54.2%	excl.	**116** 4,931 (2.4%)	**8**, 20	5.8
	≥ 19 years	Retrospective	**South Sudan (Lankien)** 2013-15	**≥ 19 years** lab. *and* clin.	¶	56.2%	excl.	**70** 1,702 (4.1%)	**8**, 21	3.3
Foinquinos 2021 (36)	Sampaio updating	Retrospective	**Brazil (Recife)** 2008-18	**< 15 years** lab. *or* clin.	-	48.7%	-	**10** 156 (6.4%)**	**1**, 1	10.0

Table 2: Key characteristics on the 12 prognostic model developments, ordered by outcome and year published. Each row corresponds to a different model.

*Including patients with missing predictor information, excluding patients with missing/excluded outcomes (unless otherwise stated).
†Number of predictor parameters (degrees of freedom); for example, a binary or linear predictor is described with 1 parameter; a predictor with 4 categories is described with 3 parameters. Candidate predictors presented in brackets are estimated from incomplete reporting.
‡Number of candidate predictors unclear. Numbers presented are inferred from the study description of extracted information and baseline characteristics.
§Number of events not disaggregated by model.
¶Age distribution tabulated by group (not reproduced here).
**Sample size excludes both participants with missing predictors and missing/excluded outcomes

Study	Model described	Model presentation and reproducibility				Model performance (c-statistic)*		Risk of bias assessment**					
	Name	Risk score presented?	Outcome risk presented?	Risk score reproducible?	Full model presented?	Internal validation (95% CI)	External validation (95% CI)	Evaluation type	P	Pr	O	A	OA
Outcome: Registry-reported mortality													
de Araújo 2012 (33)	-	Y	N	Y	N	0.756	-	dev	+	+	?	+	+
Coura-Vital 2014 (20)	-	Y	Y	Y	Y	0.80 (0.78-0.82) 0.78 (0.75-0.82)†	-	dev	+	+	?	+	+
Outcome: In-hospital mortality													
Werneck 2003 (21)	-	Y	N	Y	N	0.882	-	dev	+	+	-	+	+
Sampaio 2010 (34)	-	Y	N	N	N‡	0.895	-	dev	+	+	-	+	+
Costa 2016 (14)	< 2 years, clin. only	Y	Y	N	N	0.90 (0.84-0.97)	0.83 (0.64-1) 0.86 (0.74-0.98)	dev val (x2)	- -	- -	- -	+ +	+ +
	< 2 years, clin. + lab.	Y	Y	N	N	0.93 (0.88-0.98)	0.80 (0.57-1) 0.92 (0.84-1)	dev val (x2)	- -	- -	- -	+ +	+ +
	≥ 2 years, clin. only	Y	Y	N	N	0.89 (0.84-0.93)	0.75 (0.68-0.83) 0.88 (0.83-0.93)	dev val (x2)	- -	- -	- -	+ +	+ +
	≥ 2 years, clin. + lab.	Y	Y	N	N	0.92 (0.88-0.96)	0.79 (0.62-0.96) 0.71 (0.34-1)	dev val (x2)	- -	- -	- -	+ +	+ +
	Werneck 2003	n/a	n/a	n/a	n/a	n/a	0.75	val	?	-	-	+	+
	Sampaio 2010	n/a	n/a	n/a	n/a	n/a	0.87	val	?	-	-	+	+
	Coura-Vital 2014	n/a	n/a	n/a	n/a	n/a	0.77	val	?	-	-	+	+
Abongomera 2017 (13)	-	Y	Y	Y	N	0.83 (0.79-0.87) 0.82 (0.77-0.88)§	0.78 (0.72-0.83)	dev val (x1)	+ +	- -	- -	+ +	+ +
Kämink 2017 (35)	< 19 years	Y	Y	Y	N	0.83 (0.78-0.87)	0.72, 0.83, 0.77	dev val (x3)	+ +	+ +	- ?	+ +	+ +
	≥ 19 years	Y	Y	Y	N	0.74 (0.68-0.81)	0.72, 0.80, 0.71	dev val (x3)	+ +	+ +	- ?	+ +	+ +
Foinquinos 2021 (36)	Sampaio updating	Y	N	N	Y	0.556 0.762 (0.662-0.901)¶	-	dev	+	+	-	+	+
	Sampaio 2010	n/a	n/a	n/a	n/a	n/a	0.618	val	+	+	-	+	+

MEDECINS SANS FRONTIERES

SCIENTIFIC DAYS

Table 3: Summary of model presentations and reproducibility for model developments. Performance estimates and risk of bias assessment is presented for both model development (including updating) and external validations.

*All internal validation c-statistics relate to the apparent performance of the risk score, i.e. not adjusted for overfitting, unless otherwise stated. 95% confidence intervals are reproduced when reported. Models receiving multiple external validations report multiple c-statistics.
the external validations were assessed as having the same risk of bias across all categories and are therefore presented together.
†Split-sample (random, 2:1 development:validation).
‡Full regression equation subsequently reported by Foinquinos et al, 2021, when presenting external validation.
§Cross-validation (5-fold).
¶Assessing performance of the full model equation.
**Assessment of risk of bias is performed separately for model developments, including updating, and external validations. For every model that received more than one external validation,

+, high risk of bias; -, low risk of bias; ?, unclear risk of bias; -, not reported; c-statistic, concordance-statistic; CI, confidence interval; dev: development; n/a, not applicable for external validations only; N, no; O, outcome; OA, overall assessment; P, participants; Pr, predictors; val, validation; Y, yes.

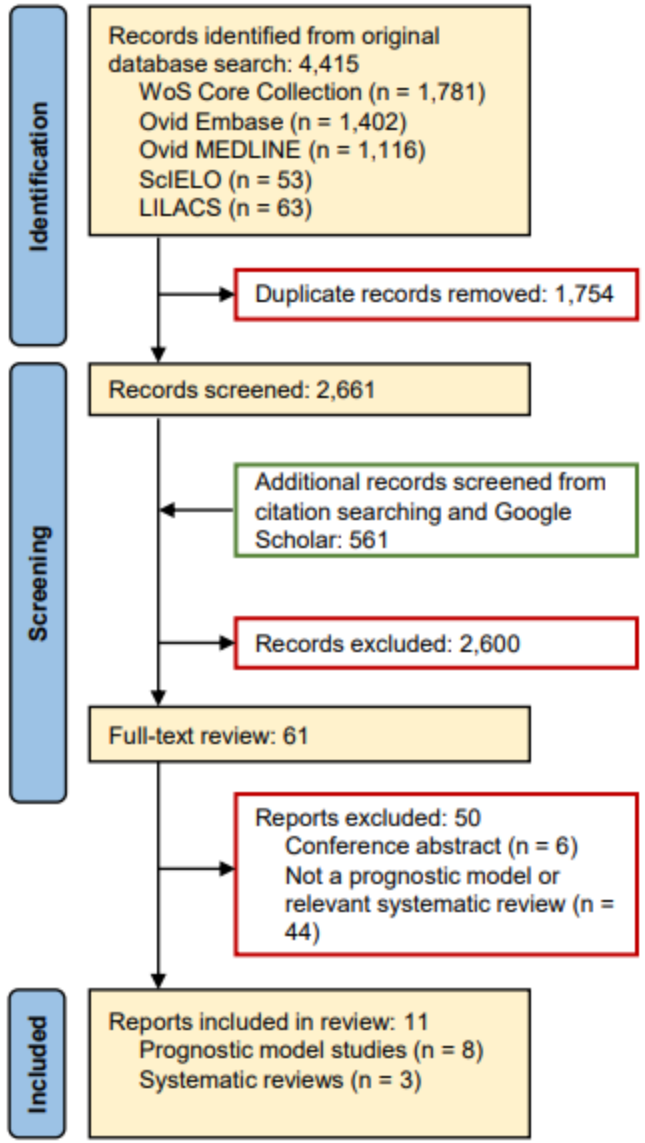


Figure 1: Flow diagram of literature search performed on March 1st 2023, and subsequent record screening.

PLOS ONE

RESEARCH ARTICLE

Development and external validation of a clinical prognostic score for death in visceral leishmaniasis patients in a high HIV co-infection burden area in Ethiopia

Charles Abongomera[1,2]*, Koert Ritmeijer[3], Florian Vogt[2], Jozefien Buyze[2], Zelalem Mekonnen[1], Henok Admassu[1], Robert Colebunders[2], Rezika Mohammed[4], Lutgarde Lynen[2], Ermias Diro[4], Johan van Griensven[2]

1 Médecins Sans Frontières, Abdurafi, Ethiopia, **2** Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium, **3** Public Health Department, Médecins Sans Frontières, Amsterdam, The Netherlands, **4** Department of Internal Medicine, University of Gondar, Gondar, Ethiopia