Published in final edited form as:

Plast Reconstr Surg. 2013 March ; 131(3): 655–665. doi:10.1097/PRS.0b013e31827c6f90.

Evidence On Prognosis

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Abstract

In the clinical decision-making process, prognostic information affords providers substantial guidance regarding disease and treatment that can be passed along to patients. Using the clinical scenario of a type IIIB open tibial fracture as an example, this article focused on how to search prognostic literature effectively and how to critically appraise prognostic studies. A well-built clinical question using helps plastic surgeons to derive information from the vast resources in an effective and time efficient manner. Subsequent critical appraisal of the collected studies is the essential step to identifying the most relevant high-quality evidence, which will provide the best prognostic information to guide patient decision-making.

Keywords

Evidence-based medicine; Evidence-based practice; Prognosis; Surgery; Outcome; Validity

The word prognosis comes from the Greek “*prognostikos*.” It combines *pro* (before) and *gnosis* (a knowing). Hippocrates used the word prognosis much as we do today, to provide important clinical information regarding possible outcomes (favorable and unfavorable) after disease or treatment.¹

In the clinical decision-making process, prognostic information provides a physician with substantial evidence that can be used to guide patients regarding disease course and treatment outcomes. To achieve the best outcome for each patient, it is necessary for a plastic surgeon to become an expert in soundly estimating the probabilities of various events that affect outcomes occurring along each therapeutic path. This is made especially difficult

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Disclosure:

None of the authors has a financial interest to declare in relation to the content of this article.

in plastic surgery where the this type of data in the literature is relatively lacking. The aim of this article is to show plastic surgeons how to approach prognostic evidence effectively, how to determine if the collected evidence is valid, and how to apply this evidence to individual patients.

CLINICAL SCENARIO

You are a consulting plastic surgeon asked to see a 22-year-old man who suffered a right-sided open tibial and fibula fracture with severe soft-tissue loss after a motor vehicle accident (MVA). He was referred for limb salvage after intramedullary (IM) nail fixation of the open tibial fracture. On examination, aside from the current injury, he is otherwise healthy with no comorbidities or other injuries from the accident. His right lower extremity shows a large soft-tissue defect spanning most of the length of the right lower extremity (**Figure 1**). The edges of the wound appear to be nonviable, but the wound itself has no gross contamination. The patient has palpable right femoral and popliteal pulses and right dorsalis pedis and posterior tibial pulses. The right foot is warm and appears to be well perfused. The capillary refill of the right toes is less than 2 seconds. The patient has minimal flexion and extension of the right toes. He has no active motion at the ankle level; however, sensation in the right foot is intact except for decreased sensation in the superficial peroneal region and saphenous nerve distribution. The patient is diagnosed with a Gustilo type IIIB open tibial fracture.

You know that there are 2 treatment options for this kind of severe tibial fracture; (1) reconstruction (limb salvage) involving fixation of tibial fractures and either local muscle flaps or microvascular free tissue transfer for coverage, and (2) primary amputation. Generally, reconstruction is the preferred choice of surgeons, despite the lack of evidence indicating better outcomes associated with reconstruction.² Additionally, both the patient and his family desire to salvage the injured limb. For these reasons, you recommend salvage. The patient and his family are happy to hear your suggestion and agree to the reconstruction. However, as you discuss the procedure and possible complications with the patient, he has a few questions: “It seems like a leg reconstruction has a lot of potential complications such as osteomyelitis, nonunion, flap failure, and subsequent secondary amputation...Doctor, how long will it be before I can go back to work?” “Of course, I would like to save my leg if possible, but I can't get that long off work. I just got a job as a construction worker and I need to work. Can you tell me which surgery would get me back to work faster?”

After the discussion, the patient realizes that salvage is not always the best choice. Now, he wants to know what to expect going forward after each treatment option, and want to learn more about predicting outcomes, particularly recovery time and probability of secondary amputation after reconstruction. Realizing that you are not sufficiently prepared to address these questions, you promise to review the evidence and discuss these issues with him the next day.

What Is A Prognostic Study?

To provide this patient useful information to select the best treatment option for him, you must be aware of the existence of several variables (e.g., patient characteristics, injury

severity, treatment timing) that can predict when patients will do well and when they will do poorly. These variables are known as prognostic factors. Prognostic factors should be clearly distinguished from risk factors, which are exposures that are associated with creating a condition or new cases (like smoking for lung cancer or drunk driving for MVAs). Prognostic factors, on the other hand, are characteristics of the clinical course that influence outcomes of conditions that already exist or interventions to treat those conditions (staging of lung cancer or injury severity score following MVAs) (**Table 1**).³⁻⁸(**Figure 2**).⁹

Like all studies, prognosis studies vary in the level of evidence they provide. A hierarchical rating system of evidence offers important guidance for the confidence you can place in the results of a given study (**Table 2**). Randomized-controlled trials (RCTs) stand at the top of the hierarchy and are most likely to provide unbiased evidence. But conducting a randomized trial of prognostic factors can be difficult, even impossible. Factors such as patient characteristic and injury severity cannot be randomized and it may be unethical to randomize patients to receive allocation of prognostic factors such as extended ischemia time or delayed debridement.¹⁰⁻¹² For these reasons, studies investigating prognostic factors are mainly observational studies, and the best such design is a prospective cohort study (prognostic level I evidence). An alternative observational study is a retrospective cohort study or a retrospective case-control study; however, these retrospective studies are of lower evidence level compared to prospective studies. In the hierarchy of evidence, case series are considered level IV evidence.

STEP 1: Perform a Literature Search

After your discussion with your patient and his family, you consult the literature to find evidence that provides prognostic information on open tibial fractures. Available online sources can be broadly categorized into those that focus on primary sources (e.g., RCTs, observational studies, or case series) and those that focus on secondary sources that provide synthesis or synopsis of primary sources, such as practice guidelines or systematic reviews (**Table 3**).

For a quick and effective literature search, secondary sources can provide a good starting point. If you can find appropriate guidelines or systematic reviews closely matching your clinical question, you can use the evidence in your clinical decision-making straightforwardly because the evidence has been pre-appraised. By using the pre-appraised evidence, a busy physician can avoid having to conduct an independent systematic review of the literature each time a clinical question is generated, and consequently save valuable time. If searching secondary sources proves unfruitful, you must turn to the primary sources.

In our example, using these databases, the combined PICO terms with their synonyms “(tibial fracture* OR tibia fracture* OR lower extremity trauma OR lower leg injury* OR limb-threatening) AND (IIIB OR IIIC) AND (limb salvage OR flap* OR amputation) AND (complication* OR prognostic* OR risk OR Outcome* OR Predictor*)” generated 49 results in the clinical study categories and 4 systematic reviews in the systematic reviews section. Scanning titles and a quick read of the abstracts identifies 14 clinical studies¹³⁻²⁶ and 2 systematic reviews^{27,28} that can potentially be useful for our clinical question. We will select the 2 systematic reviews to illustrate this scenario.^{29,30}

STEP 2: Are the results of the study valid?

Your selected articles provide information that will be helpful to your patient and his family, but in its current form the data is not easy to understand and may not even be valid. First you must appraise the methods and data to determine their validity and applicability. The key questions in the critical appraisal of an article on prognosis are listed in **Table 4**.²⁹⁻³⁴

(i) Is the sample representative and homogeneous with respect to prognostic factors? If not, were subgroup analyses performed?—The sample used in the study must match your target population as closely as possible. Any major differences may cause biases that may affect the incidence of adverse outcomes. Therefore, when evaluating studies you should carefully compare the study population with your target population on factors such as age, injury or disease severity, and other characteristics.

Saddawi-Konefka et al., report compiled results derived from 28 studies.³⁵ The patient populations were predominately male (between 68% - 89%), had a mean age ranging between 22 – 48 years, with up to 55% of patients injured in MVAs. Patients with IIIB and IIIC fractures were included and results were stratified by treatment, primary amputation or salvage attempt. Papakostidis et al., report results from 32 studies.²⁷ There is no demographic information about patients presented, but the inclusion criteria state that only adult patients were analyzed. All open tibial fractures treated with salvage were included and results were stratified by Gustilo-Anderson fracture classification. Both studies include relatively homogenous populations. Prognostic factors that may confound results, in this case treatment and fracture classification, were subject to subgroup analysis.

(ii) Are measured outcomes unbiased and objective?—Authors should clearly define their target outcomes based on the most clinically relevant measure. Objective measures, such as mortality, are the easiest to use and communicate to patients and their families. Fortunately, however, mortality is not often a relevant outcome in plastic surgery. Unfortunately, the bevy of items that make up “morbidity” are broad and often subjective. One way to make subjective measures easier to use is to previously validated and reliable scales such as the Lower Extremity Functional Scale (LEFS).³⁶ If no scale or scoring system exists, you should carefully consider how individual authors define outcomes and be wary of data from studies with poorly defined outcomes.

Papakostidis et al., examined primarily objective outcomes such as amputation rate and infection, about which there is little debate over definition.²⁷ On the other hand, Saddawi-Konefka et al., examined a wider range of outcomes, including quality of life an important, but highly subjective, outcome.³⁵ For these, the authors indicate the surveys used (SF-36, Nottingham Health Profile, General Well-Being Schedule and Fragen zur Lebenszufriedenheit Index) and provide references for the independent assessment of their applicability to your patient.

(iii) Is follow-up long enough and complete?—Follow-up should be long enough to develop a valid picture of the extent of the outcome of interest. The time period that constitutes “long enough” will vary depending on the outcome. Loss to follow-up is important and only studies that report this number should be used for decision-making. The

“5 and 20” rule is useful to determine if loss to follow-up is reasonable. If less than 5% of the study population are loss to follow-up, one can be assured that the loss has minimally impacted the results. If, however, more than 20% of the study population is loss to follow-up, caution is advised when making clinical decisions based on study findings.^{37,38}

Papakostidis et al., reported results only from studies with loss to follow-up of less than 15%, solidly within the 5 and 20 rule.²⁷ They did not, however, report mean follow-up time of the studies analyzed. Saddawi-Konefka et al., did not report information on loss to follow-up, and included studies with mean follow-up ranging from 5 months to 84 months.³⁵ The natural history of type IIIB tibial fractures can be quite lengthy; healing occurs over many months and, likewise, complications can occur long after initial treatment. Follow-up of at least a year is necessary to capture some outcomes, such as return to work. Even longer follow-up periods may be desired to fully explore coping with disability.

STEP 3: What are the results?

(i) How likely are the outcomes over time?—The purpose of prognostic information is to predict who will experience a particular outcome and who will not. The likelihood that an event will occur to a patient with certain characteristics can be expressed in a variety of ways. Most simply, events can be expressed as proportions which can easily be multiplied to include additional prognostic factors.³⁰ Likelihood can also be expressed as odds ratios or risk ratios, comparing the odds or risk of an outcome occurring in a patient that has a particular characteristic when compared to a patient without that characteristic.³¹ A ratio of 1.0 indicates that the outcome is equally likely regardless of characteristic presence. A ratio greater than 1 indicates that the outcome is more likely in patients that have the characteristic than in patients who do not; likewise, a ratio less than 1 indicates that the outcome is less likely in patients that have the characteristic. Outcomes are often reported simply as a rate (e.g., rate of secondary amputation after limb salvage is 7.3%),³⁵ however, rates convey little information and there can be important differences in prognosis within similar summary rates. Sometimes it is more informative to present how the likelihood of an outcome changes over time. This can be done with a Kaplan-Meier curve. This type of analysis presents the number of outcomes occurring over a period of time. Depending on the outcome, the time period may be minutes, days, months, or years.³³

Because your patient is especially concerned about returning to work Kaplan-Meier curves are ideal to portray the proportion of patients who return to work as a function of time after injury. These curves are created by calculating the ratio of patients who return to work divided by the total number of patients with each prognostic factor (in this case treatment: limb salvage or primary amputation). **Figure 3** shows % of patients who return to work based on choice of treatment. In patients who underwent limb salvage, 63.5% had returned to work 14.4 months after injury.²⁸ More patients who underwent primary amputation were able to return to work sooner; 73% had returned to work 13.6 months after injury.²⁸

(ii) How precise are the prognostic estimates?—A prognostic study provides only an estimate of the true risk. Therefore you need to judge how precise the estimates are. The confidence interval (CI) gives a measure of the precision (or uncertainty) of study results

when applied the population of all such patients. The 95% CI represents the range of values within which we can be sure that the true value lies 95% of the time. The narrower the CI, the more precise the estimate is. CI is affected by sample size and by variability among subjects. The larger the trial's sample size or the larger the number of outcome events is, the narrower the confidence interval and the precision is increased.

Papakostidis et al., report a mean secondary amputation rate following type IIIB fracture salvage of 6.2% with a 95% CI of 3.8%-8.6%.²⁷ The narrow 95% CI is likely a factor of the large sample size – over 3000 fractures. We believe that given this large sample size the estimates provided are quite precise and likely represent the actual prognosis following “true” rate.

STEP 4: Ensure applicability of results to your own patients

(i) Do the study patients match your own patients?—Generalizability is a concern for research of any type. Although it is important to specifically define your patient population before performing a literature search, it may not be possible to find a study with that exact sample. Comparison between your patients and those in the article, using descriptions of the study sample's demographic and clinical characteristics, is necessary. Careful interpretation of subgroup analyses is important as well. Furthermore, treatment options used in a study should be similar, if not identical, to those that you can provide. This is important to note for conditions for which there has been extensive publication. Treatment modalities change over time and what is offered today may not be exactly what was offered at the time of study.²⁹

Your patient, a 22-year-old male MVA victim with a type IIIB fracture, is on the young side of the patients presented by Saddawi-Konefka et al. His young age may result in greater functional demand and more stable long-term results, which should be communicated to him and his family. Overall, however, he is sufficiently similar to the patient samples examined that there is no compelling reason why the estimates would not apply to him.

(ii) How will the results impact my patient care?—Prognostic data often reveal certain factors that can significantly influence the outcome of a proposed treatment. Knowing the expected clinical course of your patient can help you to judge what treatment should be offered. Even if the prognostic data do not lead to a clearly superior treatment option, they can still be clinically useful. For example, the current literature offers no evidence to support superior final outcomes of either limb salvage or primary amputation for type IIIB/IIIC tibial fractures.^{28,39} However, you can provide useful outcome data for each treatment course, such as recovery time and possible complications during the treatment course.

Additionally, beyond the prescription of an effective therapy, prognostic data can be clinically useful when reassuring your concerned patient and his family as they face an uncertain future. Unfortunately, salvaging severely injured limbs does not substantially improve the patient's outcome of interest (primarily return to work) compared to primary amputation. However, even this inconclusive prognostic information can assist the patient

and his family in making important quality of life decisions and planning for the next part of their lives after the injury.

STEP 5: Resolve Your Clinical Scenario

Using these studies, you can return to your patient and his family and confidently inform them that following salvage it takes approximately 8 months until full weight-bearing and the return to work rate is more than 60% after about 14 months. These figures are each slightly better in patients who have had primary amputation, but are not significantly different. Rate of secondary amputation, as a complication after leg salvage, occurs in about 6-10% patients, and the primary prognostic factors affecting secondary amputation are infection and flap loss.

After considering this, the patient ultimately decided to undergo limb salvage. The patient and his family were disappointed to hear the poor outcomes after limb salvage operations and longer recovery time than they expected. However, the prognostic information were reassuring; the predicted outcomes allowed him to be proactive in planning the next phase of his life after this devastating injury.

Acknowledgments

Supported in part by grants from the National Institute on Aging and National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01 AR062066) and from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (2R01 AR047328-06) (to Dr. Kevin C. Chung).

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Figure 1.
A 22-year-old man with type IIIB open tibial fracture

(Lt) Standard anteroposterior radiograph of a tibial shaft fracture with intramedullary nail fixation

(Rt) Clinical photograph depicting the status of the soft-tissue and associated muscle loss

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Figure 2.
Outcome and prognostic factors for open tibial fractures
Prognostic studies examine prognostic factors to determine their relationship to possible outcomes following various therapeutic treatments.

Figure 3.

An example of Kaplan–Meier curves for 2 conditions (limb salvage and amputation) associated with rates of patients who return to work

Table 1

Examples of Risk Factors/Prognostic Factors in Plastic Surgery Field

Condition/Intervention	Risk Factors	Prognostic Factors
Malignant Melanoma ^{3,4}	<ul style="list-style-type: none"> • Genetic predisposition • Skin type (Caucasian population are at higher risk) • Presence of certain pigmented changes on the skin (freckles, dysplastic nevus) • Overexposure to UV light, sunburn in early childhood and type of work 	<ul style="list-style-type: none"> • Classification according to histopathological type • Breslow and Clark classification • Mitotic index on mm² • Presence or absence of ulceration • Number of metastatic lymph nodes and presence of satellite metastases
Diabetic Foot ^{5,6}	<ul style="list-style-type: none"> • Age (risks increase with age) • Gender (males are at higher risk) • Race (African-Americans, Hispanic Americans, and Native Americans are at higher risk) • Duration of diabetes • Other complications from diabetes • Poor blood glucose control • Smoking 	<ul style="list-style-type: none"> • Gender (males have poorer outcomes) • Delay of management • Quality of medical treatment • Surgical attitude • Inadequate level of amputation • Lack of structured prevention (patient education, general practitioners' training and cooperation between surgeons and diabetologists)
Free-flap for Head & Neck Reconstruction ^{7,8}	<ul style="list-style-type: none"> • Diabetes • Preoperative irradiation 	<ul style="list-style-type: none"> • Operation time (exceeding 10 hours)

Table 2

Levels of Evidence by Category of Study

	Prognostic Studies (investigating the outcome of disease)	Therapeutic Studies (investigating the results of treatment)	Diagnostic Studies (investigating a diagnostic test)
Level I	1. Systematic reviews [*] of Level I studies [†] 2. Prospective cohort study [‡]	1. High quality RCT a. significant difference b. no significant difference, yet narrow CI 2. Systematic review [*] of Level I RCTs (with homogenous results)	1. Testing of previously developed diagnostic criteria in series of consecutive pts (with universally applied gold standard) 2. Systemic review of Level I studies [‡]
Level II	1. Retrospective cohort study [§] 2. Lesser quality prospective cohort study (e.g., pts enrolled at different points in their disease or less than 80% follow-up) 3. Study of untreated controls from a previous RCT 4. Systematic review of Level II studies [‡]	1. Lesser quality RCT (follow-up less than 80%, no blinding, improper randomization) 2. Prospective comparative cohort study 3. Systematic review of a. Level II studies b. Level I studies with non-homogenous results	1. Development of diagnostic criteria on basis of consecutive pts (with universally applied gold standard) 2. Systematic review of Level II studies [‡]
Level III	Case control study [#]	1. Case control study [#] 2. Retrospective comparative cohort study [§] 3. Systematic review of Level III studies	1. Study of nonconsecutive pts (no gold standard) 2. Systematic review of Level III studies [*]
Level IV	Case series (no or historical controls)	Case series (no or historical controls)	1. Case control study 2. Poor reference standard
Level V	Expert opinion	Expert opinion	Expert opinion

(pt: patient, RCT: randomized-controlled trial, CI: confidence interval)

Adapted from Centre for Evidence-Based Medicine website, www.cebm.net.[†] Patients compared with a control group of patients treated at the same time and institution.^{*} A study of results from 2 or more previous studies.[‡] All patients enrolled at same point in the disease course (inception cohort) with greater than 80% follow-up.[§] Study initiated after treatment was performed.[#] Patients with a particular outcome compared to those without (failed vs successful surgeries) and reviewed for exposure, etc.

Table 3

Summary of PICO method

Method	Prognostic	Therapeutic	Diagnostic
Patients/Population (P)	What patient group? -Type IIIB/IIIC open tibial fractures -Age: 18-60	What patient group? -Same as prognostic	What patient group? -Tibial fractures
Intervention (I) (cause, prognostic factor, treatment, etc.)	Are there any prognostic factors associated with outcomes? -Patient characteristics, treatment choice (reconstruction or amputation), possible events after each treatment choice	What are the interventions? -Reconstruction	What diagnostic procedure? -Gustilo classification
Comparison (C) (if necessary)	Are there any prognostic factors not associated with outcome? -N/A (usually unnecessary)	What is the comparison treatment? -Amputation	Is there any other procedure? -AO classification
Outcomes (O)	In which outcomes are you interested? -Function, Complications, Satisfaction, Recovery time, etc	In what outcomes are you interested? -Same as prognostic	In what outcomes are you interested? - Accurate outcome prediction

Table 4

Available Sources

1. Primary sources
Citation databases
• MEDLINE (www.ncbi.nlm.nih.gov/PubMed/)
• EMBASE (www.embase.com/)
• CINHAL (www.ebscohost.com/cinahl/)
Bibliographies
• Traditional review articles/ Textbooks/ Conference proceedings/ Reviewed studies
Personal communication
2. Secondary sources
Guidelines
• National Guidelines Clearinghouse (http://www.guideline.gov/)
• AAOS Evidence-Based Clinical Practice Guidelines (http://www.aaos.org/Research/guidelines/guide.asp)
Structured Abstracts
• EBM Online (http://ebm.bmj.com/)
• ACP Journal Club (http://acpjc.acponline.org/shared/menu/about.html)
Systematic Reviews
• Cochrane Library (http://summaries.cochrane.org/)
To search several of the databases simultaneously you can use: TRIP Database (www.tripdatabase.com/)

Table 5

Evaluating an Article on Prognosis

I. Ensure the study methods (Internal validity)
i. Is the sample representative and homogeneous?
ii. Are measured outcomes unbiased and objective?
iii. Is patients' follow-up long enough and complete?
II. What are the results?
i. How likely are the outcomes over time?
ii. How precise are the prognostic estimates?
III. Ensure applicability of the study to your own patient (External validity)
i. Do the study patients match your own patients and was management similar?
ii. Was the follow-up long enough?
iii. Can the study results be used?

Table 6

Characteristics of Eligible Study

First author (Y)	Study design	Sample	Follow-up	Measured Outcomes	Results
Saddawi-Konefka (2008)	Systematic review	<ul style="list-style-type: none"> • Total 28 studies • Pts with IIIB/IIIC OTfx • All acute trauma cases • Mean age: from 22 to 48 	N/A	<ul style="list-style-type: none"> • Length of hospital stay • Complications • Rehabilitation time • QOL • Limb function • Pain • Return to work data 	<ul style="list-style-type: none"> • Length of hospital stay: 56.9D for salvage pts and 63.7D for amputees • Complications after limb salvage: osteomyelitis (17.9 %), nonunion (15.5 %), secondary amputation (7.3 %), flap failure (5.8 %) • Rehabilitation time for salvaged pts was reported as time to union (10.2M) and time to full weightbearing (8.1M). • Pain, QOL, and limb function outcomes were assessed differently among studies and could not be combined. • The proportion of patients who returned to work was 63.5 % for salvage patients and 73% for amputees.

(OTfx open tibia fractures, M: months, D: days, QOL: quality of life)