ROLE OF PROGNOSTIC SCORES IN MODERN SURGICAL DECISIONS

DÁNIEL KOLLÁR DR

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Consultants

Prof. Dr. Molnár, F. Tamás

Department of Operational Medicine

Prof. Dr. Oláh, Attila

Chair of Surgery, Petz Aladár University Teaching Hospital

University of Pécs Medical School – Clinical Medical Sciences Doctoral School (D94)

Leader of the Doctoral School: Dr. Bogár, Lajos

B-2/2013 Acute and chronic injuries of parenchymal organs and the consequences: diagnostics and therapy

Program leader: Prof. Dr. Molnár, F. Tamás

1. Introduction

Medical practice relies on previous experience in both diagnostic and therapeutic decisions. Information gathered upon examination steps may undergo numeric transformation. Rendering relevant data groups into preformed systems is the basis of clinical (prognostic) scores. Statistic methods are the tools to analyze and interpret the results. The aim we wish to reach – in medicine including surgery as well - is establishing sound diagnoses and determining more accurate prognosis.

Using a well-constructed scoring system should assist in finding the optimal decision to improve prognosis as an appropriate therapy is matched to the patient's score. However, results of the algorithm are not exclusive for other options, they only pose as a guideline with strong advices.

Prognostic scores summarize the increment or decrement of morbidity and mortality rates for a chosen intervention. The score itself estimates the outcome. Appropriately chosen variables form such a prognostic model that extrapolates the data gained from a large population to the individual. Patient data is then transformed numerically and categorized to probability (risk) groups for an event (e.g. morbidity or mortality). The inconvenient and complicated sets of data thus gain a more manageable form.

Diagnostic and therapeutic tools are constantly evolving while statistical analysis of the results creates the solid mathematic fundaments for interpretation. Numerous prognostic indices have emerged recently, while newer ones have also been forming in the present.

2. Aims

The aim of the dissertation is to answer the following questions.

1. What is the predictive value of surgical examination compared to two previously accepted prognostic scores (Alvarado score and Appendicitis Inflammatory Response score) in diagnosing acute appendicitis?
2. What are the key elements of standard score systems in guiding treatment decisions in pancreatic trauma? What is the setpoint that dictates the need for more aggressive surgical approach?
3. Where can (modified) Glasgow Prognostic Score be used in the complex oncologic-surgical treatment in cancer patients?
4. What is the effect of preoperative nutritional risk assessment based aimed clinical nutrition of oncologic patients awaiting surgery?
5. What is the substantial extramedicinal relevance of the use of prognostic indices?

3. Acute appendicitis - Appendicitis Inflammatory Response (AIR) score

Acute appendicitis remains the most common disease in emergency abdominal surgery with a life prevalence of 7%. In spite of constant improvement of radiology and laboratory measures, differential diagnosis can still be difficult.

Appendicitis Inflammatory Response (AIR) score is constructed with objective and graded diagnostic elements. The patient is categorized with the overall sum to either low, medium or high risk of acute appendicitis. Retrospective evaluation of the AIR score showed its higher prognostic value compared to the previously available Alvarado score. The aim of our study is to prospectively assess the prognostic values of surgical examination, Alvarado score and AIR score in patients with suspected acute appendicitis. Sensitivity, specificity, positive and negative predictive values are compared statistically.

3.1. Materials and methods

Data was prospectively collected between 1st January and 1st July in 2013 in Waterford Regional Hospital (Waterford, County Waterford, Republic of Ireland). Patients with acute right iliac fossa pain referred to the surgical service were included. A single page proforma was used by the surgeon on-call to register the elements of the Alvarado and AIR scores. The surgeon also categorized the patient to low, medium or high risk of acute appendicitis based on their clinical findings.

One hundred eighty-two consecutive patients were enrolled during the six months' period. Male to female ratio was 79/103 (43%/57%), with a mean age of 19.3 years [between 4 – 75 years].

Acute appendicitis was histologically proven in 67 cases (37%). Forty-eight percent of the patients (n=88) underwent surgical intervention (appendectomy in 74 cases, diagnostic laparoscopy in 14 cases). Eighty-six percent of the operations were laparoscopic. Histology did not reveal appendicitis in 16% (n=12) of the removed specimens (negative appendectomy).

3.2. Results

Alvarado score categorized the most patients to high risk of acute appendicitis (45%), while AIR score and surgical risk assessment rendered significantly lower rates there (14% and 29%

respectively, $p<0.001$). AIR score had a significantly higher specificity (97%) and positive predictive value compared to Alvarado score in the high-risk group.

Both scores and clinical assessment allocated similar rates to the low risk groups ($p=0.615$). None of the patients had complicated appendicitis in those who were deemed low risk by the scores. However, surgical assessment allocated two patients in the low risk group, who later were diagnosed with complicated appendicitis.

Complicated appendicitis was present in similar rates (≥75%) in all three high risk groups. (p=0,350).

Patients in the high risk group had significantly larger rate of complicated appendicitis if categorized by AIR score (48%) compared to the Alvarado score (19%) and surgical examination (25%) ($p=0.012$).

3.3. Discussion

Our study was the first in literature to prospectively evaluate the performance of risk estimation by Alvarado score, AIR score and surgical assessment in acute right iliac fossa pain. Our results conclude that AIR score is safe to rule out acute appendicitis. Patients deemed to low risk group can be followed up as outpatients. Hospital admission and radiology imaging is not necessary in this group. High AIR score warrants the need for surgical intervention, further examinations will not alter this decision. Radiology imaging and/or further observation is necessary in the medium risk group.

4. Classification of pancreatic trauma

Injury of the pancreas is relatively rare. According to the literature, pancreatic trauma is present in only 0.2-2% of all trauma cases, and in 2-12% of all abdominal trauma.

Early diagnosis is easy to miss, which can lead to severe acute and late complications in case of substantial parenchymal lesion. Classification of injury types, diagnostic findings and complications is a tool to ease therapeutic decisions. The key element of the diagnostic algorithm remains the need and timing of (surgical) intervention. Grading is also resourceful to facilitate statistical comparisons between different approaches (e.g. conservative management vs endoscopic drainage vs percutaneous drainage vs surgical exploration)

4.1. Materials and methods

Online literature search was carried out including Pubmed, EMBASE and Cochrane databases. Search terms were ‘blunt pancreas trauma’ and ‘blunt pancreatic trauma’ to explore relevant articles. Publications were included between 1990 and 2015. All reviews and prospective studies were examined.

4.2. Results

Classifications focusing specifically on pancreatic injury are numerous. Common feature is the emphasis on the presence of main pancreatic duct injury. Grading of injury severity and, thus prognosis is in strong connection with the integrity of the Wirsung duct. Most important classifications are as follows:

1. Organ Injury Scaling of the American Association for the Surgery of Trauma
2. Takishima classification
3. Cape Town classification
4. Frey-Wardell classification

4.3. Discussion

Pancreatic trauma usually presents with non-specific and vague abdominal symptoms and signs on both clinical examination and radiology imaging. Hours and even days can pass

between isolated (single organ) pancreatic injury and the first symptoms. This can often lead to missed early diagnosis.

Our online database search revealed only retrospective study cohorts, with barely any publications on multicenter experience. Systematic review carried out by *Haugaard et al.* failed to discover any prospective or randomized trials on the matter.

Penetrating torso injuries with hemodynamic instability need to be approached according to damage control principles. Blunt abdominal trauma – provided that hemodynamic stability is present – need to undergo complex diagnostic algorithm. These patients need to be treated in high progressivity trauma centers. The extent of radicality (endoscopic/percutaneous or surgical techniques) can be determined with the aid of the above-mentioned grading systems.

Grade I-II pancreatic injury mostly recovers with only conservative management - as in acute pancreatitis. Main pancreatic duct involvement (above Grade II) may lead to severe complications, especially if misdiagnosed in the early stage. Wirsung duct disruption can cause acute pancreatitis, pseudocyst, pancreatic fistula, retroperitoneal fluid collection/abscess. Progression can lead to multi-organ failure and even death.

Radiology imaging is not 100% reliable to detect pancreatic injury. The suspicion of main pancreatic duct injury warrants the need for ERCP even if computed tomography and/or magnetic resonance imaging are negative. If duct involvement is diagnosed, transpapillary duct stenting is indicated. Laparotomy can be limited to cases where minimally invasive reconstructive methods fail to succeed (e.g. early diagnosed Wirsung duct disruption). This diagnostic and therapeutic algorithm requires (trauma) center expertise, where high progressivity endoscopic, surgical, intensivist and interventional radiology background is available.

5. Prognosis in oncology

5.1. Glasgow Prognostic Score (GPS)

One of the cornerstones in estimating the outcome of patients with malignant tumors is accurate staging. However, individual components modulating the prognosis have been getting increasing attention lately. Nutritional and functional decline are both independent factors in predicting worse outcome. Host systemic inflammatory response [syndrome] (SIR[S]) triggered by the tumor presence has major impact on progression. Relation between SIR and cancer mortality is multifactorial and far from satisfactory understood. Key elements are well documented, such as the modulation of white blood cell count, qualitative blood count, albumin and C-reactive protein (CRP) levels. Higher CRP, lymphocytopenia and hypalbuminemia are all projecting advanced malignancy.

Patient survival data analysis led *Forrest et al* to the conclusion that combining two independent risk factors – serum CRP and albumin levels – increases accuracy in estimating disease course, thus creating Glasgow Prognostic Score (GPS). GPS is the sum of points for CRP level (1 point if CRP>10 mg/l) and albumin level (1 point if albumin<35 g/l). Zero point means better prognosis while 2 points predict the worst outcome.

Succeeding studies revealed that SIR develops nutritional and functional decline on the long run. One of its important markers is serum albumin. Modified GPS (mGPS) was introduced to express this connection. As chronic systemic inflammation (higher CRP) leads to hypalbuminemia, mGPS only counts low albumin level if CRP is above normal. In other words, normal CRP automatically results in 0 mGPS. Statistical evidence confirms that assessment of mGPS during routine oncology workup, follow-up and decision making is important.

5.2. Nutritional Risk Score 2002 (NRS 2002)

Defining malnutrition and cachexia are challenging. Optimal work-up to measure their elements does exist, but the clinical and laboratory methods are not wide-spread. Numerous nutrition state tests have emerged as an alternative to assess malnutrition. ESPEN work group has introduced Nutritional Risk Score 2002 (NRS 2002) screening. In spite of theoretic and empirical approach of previous malnutrition screenings, NRS 2002 was created using evidence-based criteria. Weight loss, nutritional impairment, abnormal body mass index and disease severity all count in a graded manner. Also, senior patients above 70 years get one additional

point upon assessment. Calculating NRS 2002 uses objective parameters, without need for laboratory testing. It is an easily reproducible, repeatable screening with no additional costs.

NRS 2002 is the graded sum of impaired food uptake (0-3 points) and disease severity (0-3 points) with one additional point in subjects above 70 years.

- 0-2 points: no risk for malnutrition
- 3-4 points: increased risk of malnutrition, dietitian work-up is advised
- 5-7 points: severe malnutrition, clinical nutrition is needed

All patients above 2 points in NRS 2002 have increased risk of postoperative morbidity and mortality and length of hospital stay, thus clinical nutrition needs to be considered.

5.3. Preoperative nutritional state assessment of oncologic patients

5.3.1. Materials and methods

Data was collected prospectively in the Chair of Surgery in Petz Aladár University Teaching Hospital, Győr, Hungary between October 2016 and November 2018.

Patients awaiting surgery for proven or suspected malignancy or inflammatory bowel disease were assessed in five groups (breast, liver, pancreas, gastrointestinal tract and thoracic surgery) (n=1609). Single page proforma was used to register demographic, co-morbidity, operation data and outcome. Primary end-point was 30-day postoperative morbidity and mortality, secondary end-point was length of hospital stay.

Enrolled patients were allocated to malnutrition risk groups using NRS 2002 (0-7 points) with telemedicine screening. In case of increased risk and severe malnutrition, oral nutrition supplement (ONS) was recommended by our dietitian. The ONS dose and composition was personally optimized according to background history and nutritional preferences.

A second nutritional survey was performed in person by the dietitian upon hospital admission. This screening allocated the patients to one of the three groups.

- **Group I:** NRS 2002 0-2 points → nutrition therapy is not indicated
- **Group II-:** NRS 2002 ≥3 points → nutrition therapy is indicated BUT the patient did not undergo adequate dose and/or period ONS prehabilitation
- **Group II+:** NRS 2002 ≥3 points → nutrition therapy is indicated AND the patient received adequate dose ONS prehabilitation for at least 7 days

Statistical analysis of groups I, II- and II+ demonstrated relationships between prevalence of malnutrition risk, overall morbidity, mortality and length of hospital stay.

5.3.2. Results

NRS 2002 deemed 95.2% of breast tumor surgery patients as not at risk of malnutrition (Group I). Patients awaiting thoracic surgery have increased risk or severe malnutrition in 40.7%. Forty-three percent of liver resection and 80.9% of pancreatic surgery patients have NRS 2002 above 2 points (increased risk or severe malnutrition).

Thoracic surgery comes with the lowest morbidity rate in Group I (no risk of malnutrition). In Group II- and II+, severe complications occurred more often than in Group I ($p>0.05$, non-significant difference). In those with elevated risk of malnutrition, adequate nutritional prehabilitation (Group II+) resulted in non-significant reduction of severe complication rate, compared to lack of nutritional support (Group II-).

Analysis of operations on the gastrointestinal tract (n=822) are as follows. Both the presence of malignant tumor and its advanced stage (surgically incurable) result in higher NRS 2002. Increased risk or severe malnutrition (NRS 2002 ≥3) are present in 71.2% of all patients. The same rate in the benign histology subgroup is 60.3%. Resections with curative intent show 67.9% increased risk, while the highest rate, 84.5% is in case of palliative resections.

Pearson test showed strong significant positive correlation ($p=0.004$) between values of NRS 2002 and the Clavien-Dindo postoperative morbidity classification.

Members of Group II- spent the most days (8.165 ±4.806) in hospital following surgery. When compared to those with increased risk and adequate preoperative nutritional support (Group II+, 7.544 ±2.887 days), the difference is not significant ($p=0.069$)

Emergency surgery cases show the worst results in NRS 2002 values, morbidity and mortality rates and length of stay as well.

Subgroup of elective colorectal carcinoma resections with curative intent (n=259, Dukes stage A, B and C) have the lowest average NRS 2002 in the gastrointestinal tract surgery cohort (2.892 ±0.841). Increased risk or severe malnutrition here was present in only 62.2%.

Mild complications presented in 19.4%, while severe complications occurred in 2.0% in Group I (no need for nutrition support). These were similar to the morbidity rates of the adequately prehabilitated Group II+ (23.3% and 2.3% respectively). Worst outcomes were registered in patients with lack of recommended preoperative nutritional support (Group II-, 26.3% and 5.1% respectively). In-between group differences were not significant with chi-squared test ($p>0.05$). In the same subgroup analysis, members of Group II+ spent the least amount of time in the hospital after surgery which is not significantly better, than Group I.

Again, Group II- presented the most unfavorable results (Group I vs Group II- p=0.006, Group II- vs Group II+ p=0.0009) showing strong significance.

5.3.3. Discussion

If patients with malignant disease undergo surgery in a suboptimal nutritional state, then even resections with curative intent can have higher failure rate. Inadequate response to surgical stress can lead to increased risk of septic complications, anastomotic leaks and overall perioperative mortality. Individualized nutritional preconditioning can ameliorate the short term (postoperative complications) and long term (complete restitution) outcome as well.

The above results demonstrate that preoperative nutritional mass screening and individualized prehabilitation of high-risk patients should and can be achieved. Professional colleges of Hungary have translated and adapted the nutritional guidelines and protocols, with advice on creating nutritional teams. However, methods are not stated and funds are insufficient. Our goal, to establish a nutritional mass screening with sustainable clinical nutrition support protocol is successfully reached.

The results of this study support strong, controlled, repeatable evidence for our conclusions. ESPEN guidelines state a series of measurable outcomes (e.g. postoperative complications, mortality and length of hospital stay) to test efficiency of perioperative nutrition screening. Our model demonstrated favorable changes in these end-points.

Increased risk of malnutrition and severe malnutrition are present in up to 62.2% of patients awaiting elective, curative colorectal resections. Palliative surgical intervention on the gastrointestinal tract is performed with 84% chance of underlying malnutrition. Eighty-eight percent of emergency bowel operations are executed on potentially malnourished patients. The latter group has the worst statistics in NRS 2002 values, Clavien-Dindo complication rates and mean length of stay as well.

Our research showed that increased values of NRS 2002 result in higher morbidity rate. This is in accordance with the observation that nutritional screening has real predictive capacity. Furthermore, higher NRS 2002 predicts more advanced cancer stage (non-significant correlation). We registered the lowest mean NRS 2002 in patients whose final histology did not reveal malignancy. NRS 2002 was higher in cancer resections with curative intent. Highest values – as expected - were recorded in the palliative surgery group.

Comparison of Groups II- and II+ has the most important clinical relevance. According to our findings, adequately prehabilitated patients (Group II+) spend significantly less days in hospital, than those without timely clinical nutrition support (Group II-). Adherence to our oral nutritional support protocol also reduced morbidity and mortality in increased risk patients. Complication rate and severity were similar in Group I and Group II+. Differences between Clavien-Dindo morbidity of Group II- and II+ did not reach level of significance. This is partially due to the discrepancy in the number of subjects in the study groups.

Our comprehensive study protocol was the first of its kind in Hungary. We can conclude that the requirement of individualized preoperative clinical nutrition is justified and must be supported in the following patient groups: all palliative operations in abdominal and thoracic surgery, all pancreatic surgery for (suspected) malignancy.

5.3.4. Systemic Inflammatory Response (SIR) and Glasgow Prognostic Score (GPS)

Malignant tumors are the cause of 7.6-8.8 million deaths every year globally. Cancer has a life prevalence of 1:3 and every fourth deaths are cancer related in the western civilizations. The phenomenon poses a huge socioeconomic burden. It is understandable that research concerning optimal decision making in planning curative or palliative treatment is of great value. Malnutrition and SIR and their shared connection with cancer progression have been thoroughly discussed – although not entirely exploited. Increasing evidence suggest that studying SIR might have more predictive value on individual outcome than the widely accepted TNM staging. Of all the studied prognostic scores, GPS with its fixed thresholds has been proven to have outstanding accuracy and usefulness. Measuring serum CRP and albumin levels suffices to calculate (m)GPS. It is available in all oncology centers and the cost is negligible compared to the complex treatment. The screening is objective and can be repeated at each step of the follow-up.

It is high time to include investigation of elements of SIR upon planning of individually optimized complex oncologic treatment instead of the sole examination of the tumor itself. Available literature has provided convincing data about the accuracy of (m)GPS, however, interventional studies have not yet emerged.

Use of the presented and studied scoring systems are encouraged in decision making in inflammatory and malignant diseases. Obviously, as an aid, not as an obligation. Treatment planning and its communication with colleagues, patients and their relatives might become easier with a solid prognostic data at hand. Clinically challenging decisions may be more

objectively justified (e.g. commencement of palliative oncotherapy with doubtful benefit, prolonging intensive care unit treatment in a hopeless scenario).

Computerized data collection will most probably enhance the prognostic models and derived scoring systems with time, leading to increasingly punctual outcome estimation. In the (near) future, hoarding of prognostic factors may result in regarding the patients as huge digitalized databases. The optimal compromise would be finding the golden ratio between computer-assisted physician decisions and physician-assisted computer decisions.

6. Findings

ad 1. AIR score is effective in estimating risk of appendicitis in the prehospital and early hospital setting. Low (0-4 points) AIR score alone is reliable in ruling out acute appendicitis. High (>8 points) AIR score is more accurate in predicting acute appendicitis than surgical risk stratification. Equivocal cases need to be further investigated/observed. Radiology imaging may be limited to the medium risk category. Predictive value of AIR score has proven to be superior in all risk groups compared to that of the Alvarado score. AIR score is useful in rationalizing hospital admissions and radiology imaging, while reducing the number of unnecessary surgeries.

ad 2. Available scoring systems are not sufficiently reliable in decision making in blunt pancreatic trauma. However, injury to the mean pancreatic duct defines early management, complications and long-term outcome. Timely diagnosis of Wirsung duct disruption is of paramount importance but - due to limited specificity, sensitivity and predictive values - none of the available radiology imaging methods are unerring. The presented injury severity scores and classifications need to be flexibly used. Minimally invasive methods are the preferred interventions, while surgical resection/reconstruction remains the last refuge.

ad 3. Incorporating (modified) Glasgow Prognostic Score in treatment decision making is justified in oncology patients. mGPS has been proven to increase efficiency in outcome prediction.

ad 4. Preoperative nutritional screening is required for patients awaiting surgery for malignancy. The presented model is feasible. Risk groups of NRS 2002 have been proven to show correlation with complication severity. Prehabilitation of patients at risk of malnutrition with clinical nutrition ameliorates outcome.

ad 5. Use of prognostic scores in general, and – especially with the demonstrated examples - in surgery increases patient security, quality of data collection and validity of scientific interpretation. Their objectivity protects patients, doctors and health providers in malpractice situations, which is not negligible. Documented risk stratification is a solid evidence in practicing expected diligence, thus benefiting us all.

7. Conclusions

Each of the presented and examined scoring systems consist of widely available and measurable components. They are objective, reproduceable and easily repeatable, and aid the clinicians in decision making with negligible additional costs. Use of the scores is feasible in outpatient clinics, hospitals and follow-ups as well. Recent and ongoing information technology developments allow us not to memorize all the components and thresholds. Computer and mobile applications can help us automatizing score calculations.

As for now, leaving diagnostic and/or therapeutic decisions to machines raise serious legal and ethical concerns. However, improving available medical evidences promotes artificial intelligence to be a valuable support for the physician in clinical decision making.

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