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Splenic biopsies are underutilized due to overestimation of bleeding risks

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ABSTRACT A critical appraisal and clinical application of Civardi G, Vallisa D, Berte R, et al. Ultrasound-guided fine needle biopsy of the spleen: high clinical efficacy and low risk in a multicenter Italian study. *Am J Hematol*. 2001 Jun;67(2):93-9. doi:[10.1002/ajh.1085](https://doi.org/10.1002/ajh.1085)

Keywords: spleen, splenic, fine-needle biopsy

Clinical Context

The patient was a middle-aged man, admitted from the ED for persistent abdominal pain and bloody diarrhea. He had been given oral vancomycin by an outside hospital ED about a week prior to treat *C. difficile* colitis, but his symptoms had not improved. The patient had a history of recurrent *C. difficile* infections, Crohn's disease, and a small splenic mass.

The patient was admitted into isolation on a general practice (GP) floor and both the gastroenterology (GI) and infectious disease teams were consulted. His *C. difficile* toxin was negative and he was started on IV Solu-Medrol (methylprednisolone) for his Crohn's disease. After four days with no response to the steroids GI recommended switching to a TNF-alpha inhibitor. However, due to the concern that the splenic mass was a lymphoma, GI wanted a definitive diagnosis before proceeding. On hospital day five, both surgery and interventional radiology (IR) were consulted about getting a definitive diagnosis. Surgery did not consider the patient a surgical candidate because of his active inflammation and steroid use, and they recommended consulting IR. IR would not do a biopsy due to concern that the bleeding risk was too high. Over the next three days the different departments debated the best course of action, and the patient grew increasingly frustrated as he was concerned about the splenic mass and felt it was not being addressed. On hospital day nine he was noted to have an increased WBC count, so a stool sample was taken for *C. difficile* toxin. That night he left against medical advice (AMA) to "seek care elsewhere."

The next day his *C. difficile* toxin came back positive, so he was called to come back into the hospital for treatment and he was readmitted. While the patient began treatment for the *C. difficile*, the team heard about a "cowboy" in the IR department who would often attempt procedures other providers had refused. This doctor agreed to consider trying the biopsy after seeing the mass firsthand on the IR table. The patient was very happy the mass was being addressed and was not concerned with the risks of the biopsy. The fine needle splenic biopsy was performed 14 days after initial presentation to the ED with a 20 gauge needle; four specimens were gathered, and no complications occurred.

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Clinical Question

Is the complication rate of image-guided percutaneous splenic biopsies overestimated by physicians compared to the complication rate of solid abdominal organ biopsies?

Research Article

Civardi G, Vallisa D, Berte R, et al. Ultrasound-guided fine needle biopsy of the spleen: high clinical efficacy and low risk in a multicenter Italian study. *Am J Hematol*. 2001 Jun;67(2):93-9. doi:[10.1002/ajh.1085](https://doi.org/10.1002/ajh.1085)

Literature Review

This article was chosen for review by searching the PubMed database for articles containing the phrases “splenic biopsy” and “spleen biopsy.” Studies were then excluded based on sample size (<100 patients) and whether they addressed the clinical question. Among the remaining articles was a meta-analysis conducted by McInnes, Kielar, and Macdonald in 2011¹. This meta-analysis included a significant number of the remaining studies and seemed to encapsulate the extent of current research on image-guided splenic biopsies. The complication rate arm of this meta-analysis included nine studies with a total of 859 splenic biopsies (fine needle and core biopsies). Of the included studies, “Ultrasound-Guided Fine Needle Biopsy of the Spleen” by Civardi et al. contributed over half of the biopsies (453/859) and had the second highest STROBE score of 17¹⁻³. This paper was chosen for critical appraisal because it is a driving force in the current understanding of the risks of image-guided splenic biopsies.

Civardi et al. concluded the overall complication rate for splenic biopsies “was low (but not negligible), with a percentage of complications less than 1% and no deaths”². The study also acknowledges that splenic biopsies are still widely considered to be dangerous by most physicians especially in the US.

The meta-analysis reported the major and overall complication rates for splenic biopsies to be 2.2% and 4.2%¹. The meta-analysis is in alignment with Civardi et al. and concludes that the complication rate for splenic biopsies in the current standard of practice is comparable to those for both liver (0.5-3.3%) and kidney biopsies (0.7-6.3%)¹. This is unsurprising because the Civardi study contributed most of the data for the analysis. The study also notes the morbidity and mortality of splenic biopsies is considerably lower than the most likely alternatives, splenectomies¹.

Additionally, in a study completed after the meta-analysis, which looked at 137 patients with isolated splenomegaly undergoing CT-guided fine-needle biopsy, Tokue et al. reported only three adverse events⁴. This study is particularly valuable because it may be more relevant to modern biopsy techniques, helping to confirm the results from the meta-analysis and older studies^{1,5}.

Critical Appraisal

While this study enjoys the advantage of having the largest number of biopsies performed, it has significant flaws. The first major disadvantage of this study is that it was designed as a retrospective review. This leads to the problem that the patients were not randomized, and there were no control groups. Another problem with the study methodology is a lack of selection criteria for the centers. The only information about how the locations were selected was that they must have had at least 10 years of experience using this biopsy technique. This significantly impacts the validity and how generalizable the study is because there is no way to know if this includes all the Italian centers that have been open for at least ten years, or whether they were chosen based on their low complication rates. A further problem with the choice of cases is that there are no criteria for the inclusion of individual cases. Chosen cases could include the first cases performed at a center, all the cases, or only the most recent. This could have dramatic implications, especially for the complication rates, which would be expected to decrease with experience. These issues leave the study with no protection from confounding variables, and expose it to a myriad of selection biases. The differentiation between major and minor complications in this study is reasonable; however, it would be helpful to know how long an observational period or hospital stay must be before it is considered prolonged. This would allow better understanding of the complication rate, and would help make it more generalizable, because the standard practice for length of hospitalization or observation can vary based on geographical area and over time.

Another unfortunate limitation is that there is no comparison or mention of the complication rate for other definitive diagnostic procedures in similar patients. This makes the study less useful when trying to decide the best procedure to diagnose a splenic lesion.

From the 398 cases reviewed, the numbers needed to harm (NNH) for major (3), minor (18), and total complications (21) were 132, 22, and 19 respectively. In other words, 132 percutaneous image-guided splenic biopsies would need to be performed, on average, for one patient to experience a major complication. However, these numbers are not particularly useful because the biopsy is being compared to no biopsy with an assumed complication rate of zero. The appropriate comparator for this calculation is the number of complications due to a lack of diagnosis, which is unknown. As calculated, the NNH does give a partial effect size about the risk of the procedure itself.

Additionally, the positive and negative likelihood ratios help illuminate the diagnostic value of splenic biopsies. They were 113.8 [95% CI, 28.6-453.1] and 0.10 [95% CI, 0.06-0.16] respectively. This means that a patient similar to ours with a low pretest probability of lymphoma (5%) would have an 86% post-test probability with a positive test or 0.5% with a negative test. This highlights the usefulness of splenic biopsies as diagnostic tests and shows the benefit may outweigh the risk even with the low possibility of complication.

The study earns a Level of Evidence of Level 3 from the Oxford Centre for Evidence-Based Medicine 2014. It attempts to answer questions about the efficacy of a diagnostic test and how frequently complications occur. For examination of the diagnostic value, only a small proportion of the cases had a gold standard to compare to, and 80.4% were controlled with follow-up data. The frequency of complications was determined by a non-random local sample also consistent with Level 3 evidence.

Clinical Application

While the study may not have been ideally designed, it does reveal an area where theory and assumptions of risk may be guiding treatment rather than available evidence. This research is of critical importance to patients, because they cannot make an informed decision to undergo a procedure without knowing the risks. Also, physicians may be under-performing these biopsies because the conventional wisdom and historical use of larger bore needles⁵ has led to widespread overestimation of the complication rate. This may lead to significant morbidity and mortality through the potential delay in diagnosis, worse prognosis at discovery, or subjection to procedures that place patients at higher risk. If the findings of this paper were more widespread, it might have taken less time for our patient to get his splenic biopsy, and not required consulting a specific physician. This would have led to considerably less frustration on the part of our patient and potentially prevented him leaving AMA with an active *C. difficile* infection. Unfortunately, the result of his biopsy could not rule out lymphoma. However, he had no complications from the procedure. This highlights the safety of the procedure and that the possibility of additional testing needs to be addressed with patients undergoing any diagnostic test.

Take Home Points:

- 1.) The risks and benefits of all aspects of medicine should be evaluated objectively if possible.
- 2.) Therapies that are widely considered safe or risky often lack sufficient objective high quality research to justify those beliefs.
- 3.) Special effort must be made by physicians to determine if the patient is benefiting from subjective experiences or being harmed by unacknowledged biases.

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