EVALUATION OF INFLAMMATORY MARKERS AS PREDICTORS OF HOSPITAL STAY AND UNPLANNED READMISSION AFTER COLORECTAL SURGERY

DAVID M. KRUPATA, DEBORAH S. KELLER, HODA SAMIA, JUSTIN LAWRENCE, IZI OBOKHARE, ERIC MARDERSTEIN, KAREN M. BRADY, CONOR P. DELANEY

Division of Colorectal Surgery, Department of Surgery, University Hospitals-Case Medical Center, Cleveland, Ohio

Kierownik: C. P. Delaney, MD MCh PhD FRCSI FACS FASCRS

Hospital length of stay (LOS) and readmissions continue to be expensive and unexpected events following colorectal surgery (CRS) whether patients follow enhanced recovery pathways or traditional care. Predictors of these adverse events could facilitate identification and optimization of CRS patients.

The aim of the study was to examine the impact of white blood cell count (WBC) and C-reactive protein (CRP) levels as predictors of delayed recovery or hospital readmission following CRS.

Material and methods. Patients undergoing laparoscopic or open abdominal colorectal surgery by a single surgeon were managed using standardized enhanced recovery pathways. Those with postoperative day 2 CRP and white blood cell values were evaluated. Outcomes included 30-day hospital readmission rates and postoperative length of hospital stay.

Results. CRP values were available for 193 patients (86 Male, mean age 58.6 years). Ninety-nine patients had surgery for colon cancer, 23 for Crohn’s disease, 19 for ulcerative colitis, 31 for diverticulitis and 18 for other reasons. Twenty patients (10.4%) were readmitted to the hospital within 30 days of surgery. POD2 CRP accurately predicted short length of hospital stay (p< 0.01). Average CRP was 6.3 in the LOS of ≤ 3 days or less, and 11.7 in patients with LOS >4 days. The mean CRP of the readmission and non-readmission groups was 11.8 and 9.9, respectively (p=0.29). The average POD 2 WBC of the readmission and non-readmission groups was 10.6 and 9 respectively (p=0.01).

Conclusion. A low POD2 CRP level was correlated with a shorter LOS, but it did not predict readmission. Conversely, POD2 WBC, and the difference in WBC from baseline were associated with readmission. These markers may be useful indicators to predict suitability of early discharge in an ERP. Further evaluation in prospective trials is warranted.

Key words: C-reactive protein, enhanced recovery pathway, readmission, colorectal surgery

Hospital readmission continues to be an unpredictable event following colorectal surgery (CRS). Rates of unplanned hospital readmission following major abdominal surgery have been reported between 10-12% (1-4). Readmission following colorectal surgery specifically has been reported between 8-20% (4-8), tending to be in the order of 11% after segmental colectomy and up to 20% after pelvic surgery (8). Within this 8-20% there are multiple subgroups. Goodney et al. described an 11% 30 day re-admission rate following colectomy for cancer when the Medicare database was reviewed from 1994-1999. While experimenting with enhanced recovery pathways, Anderson et al. showed a difference in readmission rates following colonic surgery of 20.1% after a planned 2-day fast track compared to 11.3% with a planned 3 day fast track hospital stay (2). Specific to laparoscopic colon and rectal operations, a 10% readmission rate has previously been described (4). Kariv et al. identified factors associated with hospital re-admission within 30 days of discharge follow-
ing intestinal surgery including chronic obstructive pulmonary disease, previous anticoagulation, peri-operative steroids, and discharge disposition (2).

With the advent of enhanced recovery pathways, length of hospital stay (LOS) has decreased without any increase in the percentage of hospital readmission within 30 days of surgery (9, 10, 11). Further, in laparoscopic colorectal surgery, early discharge is not associated with early readmission compared to open surgery (4), and early discharge has been associated with lower readmission rates (6).

When using enhanced recovery pathways, patients are discharged when standardized discharge criteria have been met. At the current time there are no defined predictors of readmission. C-Reactive Protein (CRP) is an acute-phase inflammatory reactant that increases in response to tissue injury or infection; CRP is used clinically to identify inflammation. While a non-specific marker, previous reports have identified CRP as a predictor of post-operative complications in CRS (13, 14). Welsch et al found CRP peaked on post-operative day (POD) 2 following colorectal surgery (14). In this study we set out to evaluate CRP and WBC as a potential predictor of early recovery or hospital readmission following colorectal surgery.

MATERIAL AND METHODS

A retrospective review of a prospective, Institutional Review Board approved departmental database was performed to identify all patients undergoing CRS by a single surgeon between July of 2007 and November of 2011. Both open and laparoscopic cases were included. All patients were part of an established enhanced recovery protocol, with standard discharge criteria previously described in the literature (6). Medical records were reviewed for additional clinical variables. Minors, patients with incomplete medical records, and patients transferred to the surgical intensive care unit for post-operative care were excluded from the analysis. Data recorded included: sex, age, pre-operative diagnosis, procedure performed, type of anastomosis performed, pre-operative and post-operative CRP levels, pre-operative and post-operative whirr blood cell count (WBC), Surgical Intensive Care Unit (SICU) stay, complications, discharge destination, and reason for readmission, if applicable. Primary outcome measures were hospital readmission within 30 days of surgery and hospital LOS. LOS was defined as nights spent in the hospital. For example, a surgery performed on a Monday with a discharge on Thursday would be a LOS of 3 days.

Data analysis was performed utilizing student paired t-test's, with a p value of < 0.05 considered statistically significant. Data analysis was performed with R statistical program (Vienna, Austria). Receiver operating characteristics (ROC) curves were created by calculating sensitivities and specificities for POD2 CRP values of 5, 8, 10, 12, and 15 for LOS 3 days or less vs LOS 4 days or more and WBC vs readmission rates. Sensitivity was then plotted against false positive rate (1-specificity). All reported CRP values are in mg/dl and WBC values are in 10^9/L.

RESULTS

193 patients met inclusion criteria for the analysis. The median age of the patients was 58.6 (range, 18 to 91), and 55% (n = 107) were female. Demographic data is detailed in tab. 1. The median postoperative length of primary hospital stay (LOS) for all patients was 5.6 days (range 2-39). The median LOS for readmitted patients was 6.3 days and 5.5 for patients who did not require readmission. Using linear regression modeling, length of stay was
not statistically significant as a predictor of readmission in this series (p=0.46).

Twenty patients (10.4%) had an unplanned readmission within 30 days of the operation. One patient had a planned readmission and was therefore excluded from analysis of the readmission group. Reasons for readmission included ileus/obstruction (8), anastomotic leak/pelvic collection (two) surgical site infection (two), intra-abdominal abscess (two), surgical site infection and intra-abdominal abscess (one), dehydration (one), constipation (one), bleeding anastomosis (one), and two patients returned with an upper gastrointestinal bleed. Three patients required reoperation (1.6%). One patient had a drain placed by interventional radiology. Readmissions occurred on postoperative days 5 through 30. Mean LOS during a hospital readmission stay was 7.6 days with a median of 5 days (range 2-34 days). The 30-day postoperative mortality rate was zero.

Of the 193 patients who had POD2 CRP levels, 162 (83.9%) had pre-operative CRP levels, 180 (93.3%) had a pre-operative white blood cell count (WBC), 182 (94.3%) had post-operative day 2 WBC and 180 (93.3%) had both pre and post operative WBCs. Laboratory values are detailed in tab. 2. The changes between pre and postoperative CRP and WBC values were analyzed. The mean pre operative CRP level was 1 (±1.9). The mean change between the pre and postoperative CRP was 8.7 (±6.5). The change between pre and post-operative CRP in the non-readmitted group was 8.4 (±6.3) and in the readmitted group were 10.7 (±7.6). There was no significant difference between the readmitted and not readmitted groups when comparing the change between pre and post op CRP (p=0.25). One hundred eighty patients had pre and post-operative WBCs recorded. The mean difference between pre and postoperative WBC for all patients was 1.7 (±3.5). The difference in pre and postoperative WBCs in the readmitted group was 3 (±4.2) and 1.5 (±3.4) in the non-readmitted group (p=0.15). Using linear regression modeling, POD2 CRP did not predict 30-day readmission while an elevated WBC on POD2 was a significant predictor of readmission (tab. 3).

The second primary outcome measured was LOS (tab. 4). Fifty-eight patients had a LOS of 3 days or less and 135 had a LOS of 4 days or more. Comparing patients with a LOS of 3 days or less versus LOS of 4 days or more the mean POD2 CRP was 6.3 (±4.5) vs 11.7 (±7.2), respectively (p<0.01). Comparing POD2 WBCs between these same groups the mean POD2 WBC was 8.5 (±3.4) vs 9.4 (±3.3) (p=0.08). Comparing pre and postoperative CRP levels between groups we see a mean change of 5.6 (±4.3) in patients who stayed less than 3 days vs 10.2 (±6.9) in the LOS of 4 days or more group (p<0.01). The difference in pre and postoperative WBC between the groups is 1.3 (±4) vs 1.9 (±3.3) (p=0.33).

Table 2. Relationship between CRP, WBC Count and Readmission

<table>
<thead>
<tr>
<th></th>
<th>Readmitted</th>
<th>Not Readmitted</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>mean (± sd)</td>
<td>(n)</td>
</tr>
<tr>
<td>POD2 CRP</td>
<td>20</td>
<td>11.8 (7.7)</td>
<td>173</td>
</tr>
<tr>
<td>Δ Pre &amp; POD2 CRP</td>
<td>18</td>
<td>10.7 (7.6)</td>
<td>144</td>
</tr>
<tr>
<td>POD2 WBC</td>
<td>20</td>
<td>10.6 (2.5)</td>
<td>162</td>
</tr>
<tr>
<td>Δ Pre &amp; POD2 WBC</td>
<td>20</td>
<td>3.0 (4.2)</td>
<td>160</td>
</tr>
</tbody>
</table>

Table 3. Linear Regression Modeling for CRP and WBC as Predictors of Readmission

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>POD2 CRP</td>
<td>1.04 (0.97-1.10)</td>
<td>0.23</td>
</tr>
<tr>
<td>Δ Pre &amp; POD2 CRP</td>
<td>1.05 (0.98-1.13)</td>
<td>0.17</td>
</tr>
<tr>
<td>POD2 WBC</td>
<td>1.12 (1.00-1.25)</td>
<td>0.05</td>
</tr>
<tr>
<td>Δ Pre &amp; POD2 WBC</td>
<td>1.11 (0.97-1.25)</td>
<td>0.10</td>
</tr>
</tbody>
</table>
Table 4. Relationship between CRP, WBC Count and Length of Stay

<table>
<thead>
<tr>
<th>Length of Stay</th>
<th>3 days or less</th>
<th>4 days or more</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>mean (± sd)</td>
<td>(n)</td>
</tr>
<tr>
<td>POD2 CRP</td>
<td>58</td>
<td>6.3 (4.5)</td>
<td>135</td>
</tr>
<tr>
<td>Δ Pre &amp; POD2 CRP</td>
<td>53</td>
<td>5.6 (4.3)</td>
<td>109</td>
</tr>
<tr>
<td>Δ Pre &amp; POD2 WBC</td>
<td>57</td>
<td>8.5 (3.4)</td>
<td>124</td>
</tr>
<tr>
<td>POD2 CRP</td>
<td>57</td>
<td>1.3 (4.0)</td>
<td>123</td>
</tr>
</tbody>
</table>

On the ROC curve, sensitivities for POD2 CRP as a predictor of discharge in 3 days or less for values of 5, 8, 10, 12, and 15 were 0.51, 0.66, 0.75, 0.85 and 0.96 respectively. Specificities for CRP as a predictor of discharge in 3 days or less for values of 5, 8, 10, 12, and 15 were 0.80, 0.67, 0.52, and 0.30 respectively. Total area under the ROC curve for fig. 1 is 0.72. For fig. 2, sensitivities for POD2 WBC as a predictor of safe discharge without readmission for values of 5, 8, 10, 12, and 15 were 0.06, 0.45, 0.70, 0.86, and 0.94 respectively. Specificities for POD2 WBC as a predictor of safe discharge without readmission for values of 5, 8, 10, 12, and 15 were 1, 0.84, 0.47, 0.32, and 0.05 respectively. Total area under the ROC curve for fig. 2 is 0.66.

**DISCUSSION**

Enhanced recovery pathways are being used more widely and discharge is being guided by standardized criteria and physician experience. Quantitative markers would be useful adjuncts aid prediction of adverse events, such as re-admission, and the decision making process for early discharge. Elevated post-operative CRP levels have been noted in abdominal infection in colorectal surgery (12, 13). If CRP or WBC could reliably predict recovery, this might help in the application of postoperative care pathways and timing of discharge, with potential for decreased health care costs and decreased readmission rates. We performed an initial trial to evaluate whether WBC and CRP would predict readmission or length of stay.

Other studies have demonstrated the role of CRP as an outcome predictor. Cappabianca et al. evaluated CRP levels cardiac surgery, finding higher in-hospital mortality (8.2% vs 3.4%, odds ratio (OR), 2.61; p = 0.02), postoperative infections (16.5% versus 5.1% OR, 3.25; p = 0.0001), and higher re-hospitalization rates (73.6% ± 6% versus 86.5% ± 3.2%; OR, 1.82; p
in the group with elevated CRP levels (15). A recent meta-analysis reported elevated CRP is considerably valuable in the diagnosis and prognosis of postoperative infections (16). To our knowledge, this is the first report of using the CRP value as a predictor of readmission or early recovery.

In our study, 20 (10.4%) patients returned for unplanned readmission within 30 days of surgery. There was no significant correlation to POD2 CRP or change between pre and postoperative CRP when compared to non-readmitted patients. It is possible that the higher baseline CRP levels in colon cancer (17) and inflammatory bowel patients may make the single CRP measure inadequate to detect significant change. In contrast, POD2 WBC and the change between pre and postoperative WBC were significantly different in those being readmitted. Readmitted patients had a mean difference in pre and postoperative WBC of 3.3 versus 1.2 in the non-readmitted group. We also found a statistically significant relationship between LOS and POD2 CRP, as patients with LOS of 4 days or longer had a higher CRP, 11.7, than patients with a LOS of 3 days or shorter, 6.3 (p<0.01). WBC on the other hand did not correlate with LOS.

The finding that an elevated POD2 CRP is associated with a longer hospital stay suggests that POD2 CRP may be used to predict recovery and infers potential implications in clinical practice. Our findings raise the possibility of adding a quantitative biochemical marker into the equation for enhanced recovery pathway discharge criteria. By predicting those who can safely be discharged early, re-admission rates could be lower, reducing overall costs. By identifying which patients are not safe for discharge, or are at risk for readmission, further observation or testing can be performed.

With only a single postoperative CRP and WBC levels we were still able to identify statistically significant differences in LOS and readmission, respectively. We chose POD2, as our goal is generally to discharge suitable patients at 48-72 hours after surgery. Nevertheless, this does raise the question of whether or not additional postoperative testing should be employed to assist in determining discharge eligibility. Ultimately, whether or not the utilization of post operative CRP levels to aid in post operative care pathways or discharge requires further study, but is potentially an exciting avenue for further prospective trials.

From the perspective of choosing WBC and CRP values which, when taken on POD2, permit safe discharge, we created ROC curves to estimate what these values potentially are. In fig. 1, a ROC curve comparing POD2 CRP and LOS, a CRP level of >12 on POD2 would indicate that with >80% sensitivity a patient will require a prolonged hospital stay even with an enhanced recovery pathway. To predict readmission, an ROC curve was created to evaluate WBC and readmission rates (fig. 2). With this ROC curve, a POD2 WBC of 12 predicts readmission with >80% sensitivity. While using POD2 CRP and WBC values of <12 as indicators of safe discharge with an enhanced recovery pathways made not be ideal based on a retrospective study, it gives us values based on the ROC curves for evaluation in future prospective studies.

Inherent in retrospective reviews are limitations. Limitations in our study include that other factors affecting discharge may not have been noted as we were limited to a database and chart review. Additional limitations include our moderate sample size. When reviewing a primary outcome measure that is only around 10% of a study population, there is demand for a larger study size in order to power the study, nevertheless, these results provide interesting and novel data in a reasonably large population of patients. Lastly, we were limited by the fact that not all patients with POD2 CRPs had pre-op CRPs, WBC or POD2 WBC. A prospective study with uniform laboratory testing and clinical discharge criteria would certainly diminish the limitations encountered in the study.

**CONCLUSION**

Insight into potential indicators of hospital readmission and post operative recovery are important as we try to standardize perioperative care and optimize recovery after surgery. In this study, POD2 CRP level was associated with a short hospital stay, although it did not predict readmission. Evaluation of CRP and WBC on POD2 with comparison to baseline may be a useful indicator of suitability for early discharge in patients following enhanced recovery pathways.
REFERENCES