Predicting effect of CRP on early diagnosis of side effects after surgery of Gastrointestinal tract

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Abstract:

Introduction:

Infectious side effects Specially in form of infections after surgery including: LEAK anastomosis after surgery of GI system (Gastrointestinal tract) is the main factor for serious morbidity. Systematic inflammation markers including: CRP and counting white blood cells were reported that may lead to early diagnosis; meanwhile, the relative prediction test is not clear.

Objective: Evaluating and determining value of CRP anticipation for early diagnosis of side effects after elective surgery of GI system (Gastrointestinal tract)

Materials and Method:

Counting white blood cells (WBC) and CRP on day before surgery and 6 days after surgery among 189 patients having 227 cases of anastomosis of GI system that were gone under elective surgery of GI system within the year 2016 and 2017 was measured and then the patients from viewpoint of SSI infection in northern part of LEAK anastomosis and infection were gone under surgery and RSI including: Side effects out of Site of surgery (emboli of lungs and MI pneumonia and UTI) were examined

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Results:

In this study 189 patients with sum of 227 anastomosis of GI system were considered; in which, 164 cases (86.7%) did not have side effects and 9 cases (4.7%) had side effects of LEAK anastomosis and 6 cases had infection of SSI (3.1%) and 11 cases had other side effects (5.8%) and on third day, CUTT CRP OFF with amount of Mg/L 136 showed highest sensitivity for anticipating side effects (100%) and by AUC was 0.5 in ROCK curve and this threshold was accompanied with increasing duration of hospitalization in hospital and morbidity

Conclusion:

In patients having elective surgery of anastomosis with GI system, measuring level of CRP on third day after surgery is useful for anticipating site of surgery (LEAK anastomosis)

Introduction:

In spite of advancements in surgery and medical care, controlling infections and using preventive antibiotics, the issue of infectious side effects is still one of the main reasons of morbidity after resection of Gastrointestinal tract. The general side effects is nearly 30% and the level of morbidity for surgery is nearly 3% to 4% (1,2). Generally, infections after surgery are divided into 2 groups including: SSI (surgical site infection) and Repetitive strain injury (RSI) (3). SSI is classified into 2 groups including: infections in site of wound and infections in organ (LEAK anastomosis and Ascites). RSI consists of UTI pneumonia, Septicemia, antibiotic enterocolitis and infection of central vein (4). LEAK anastomosis is the most serious infectious and has relationship with increasing mortality (5-6). LEAK anastomosis may be available at clinical stage on hidden basis or may be revealed within 8 to 12 days after surgery when the patient is critically ill (5,7). Moreover, it is revealed that LEAK anastomosis is accompanied with long lasting effects and enfeebling body (8-9). Thus, specific side effects of LEAK anastomosis for patients (either short-term or long-term side effects) may be catastrophe for patient. Obviously, if such patients are early diagnosed, it may prevent from the LEAK stool inside of Peritoneum and Sepsis. There are increasing number of studies that inflammation response of sepsis by using

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acute phase protein specially CRP while surgery, maybe useful for recognizing patients faced with danger of infections after surgery. In spite of researches in this field, still there is controversial issues for finding standard method for finding side effects after surgery specially LEAK anastomosis. CRP is regarded as acute phase marker protein (10) and measuring CRP is an accessible test that is widely used for diagnosing infection and controlling treatment. CRP is a marker for infection after surgery for recognizing LEAK anastomosis in Colorectal surgery (10-11). There are some studies in relation to assessment of CRP for surgery that may useful for recognizing patients faced with danger of infection of Gastrointestinal tract. In the study of Matis and et al 231 patients were gone under cancer colorectal surgery and 32 patients reported LEAK and in this study increasing level of CRP on third day after surgery with threshold of 190 mgr/l was reported (11). In the study of Velsh et al, 48 patients with similar infectious side effects and 48 patients without infectious side effects were gone under cancer rectum surgery and we observed that there is relationship between increase in level of CRP on third day after surgery with infectious side effects and the suitable threshold for anticipation was reported as 140mg/l (12). In other study performed by Matis and et al, 32 patients were gone under cancer rectum surgery and anterior resection and there was early increase in level of CRP as strong indicator for LEAK anastomosis (11). In the study of Corner and et al on 231 patients gone under colorectal surgery, there was increase in level of CRP on third day after surgery with anticipating threshold of 190 mg/l with abdominal infections (13). In the study of West and et al on 342 patients gone under cancer colorectal surgery, there was long-term increase in CRP without reducing before creating LEAK anastomosis (14). In the study of Ortega and et al on 133 patients gone under elective colorectal surgery, there was increase in level of CRP on 4 days after surgery with anticipating threshold of125mg/l with LEAK anastomosis (15). In the research of Mak Gi et al. on 160 patients gone under cancer colorectal, there was increase in level of CRP on 4 days after surgery with anticipating threshold of 145 mg/l with infectious side effects (16). In the study of Vosho et al on 1187 patients gone under resection with cancer colorectal, the level of CRP higher than 123mg/l on 4 days after surgery increased the doubt for inflammation side effects (17). In the study of Janathan 454 patients referring to royal clinic of Glasco for cancer colorectal on Jan 1997 until Feb 2007, it was shown that 120 patients i.e. (26%) had side effects after surgery and 104 patients had infectious side effects including: 53 patients had RSI, 25 patients had wound infection and 26 patients had LEAK anastomosis (18), there were 16 non-infectious

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side effects including: 2 cases of Pulmonary embolism, 4 cases of AF, 3 cases of Acute Coronary Syndrome (ACS), 5 cases of myocardial infarction (MI) and one case of Urinary Retention and one case of stomal ischemia. In comparison to patients who did not have side effects after surgery or patients with surgical site infection (SSI), the SSI group showed higher level of WBC and CRP on 3rd or 7th day after surgery. In comparison to patients without side effects after surgery with Repetitive strain injury (RSI) patients, the RSI group on 2nd to 7th day after surgery showed higher level of WBC and CRP. In this study the difference between third day after surgery with CRP threshold level of 170mg/l with sensitivity of 74% to 82% and specialty level of 50% to 80% there is ability of anticipating infections. Moreover, on 4th day after surgery on sensitivity between 54% to 77% and specialty level of 75% to 845 there is ability of anticipating infections (10,18). The main goal is predicting effect of CRP on early diagnosis of side effects after surgery of Gastrointestinal tract.

Materials and Methods:

In a fundamental, applied, analytic and foresighted study, all persons gone under elective surgery of Gastrointestinal tract and anastomosis were examined who referred to Imam Hossein hospital during 2016 and 2017. The elective surgeries of GI tract are including: anastomosis of Esophagus, stomach, small intestine, colon and rectum. Moreover, the properties of patients including: Age, sex, background disease, reasons of surgery were collected within basic foresighted surgery databank and the patients were divided based on method of anastomosis including: manual suture, surgical stapler or both of them. Patients that were gone under Loop Colostomy for creating defecation canal, patients have gone under emergency surgery, patients having infection side effects including: Inflammatory Bowel Disease(IBD) were eliminated from this study. Patients entered to this study; on day before surgery the level of their blood Albumin was measured and in case of low level of Albumin, through prescribing Albumin, its level was reached to normal level of 3.5. Then on first, second, third, fourth, fifth and sixth day after surgery, the level of CRP and WBC in blood serum of patients was measured. Before surgery, the entire patients received prophylaxis Heparin or Clexane for treatment of DVT. Moreover, patients before surgery, received prophylaxis antibiotics (one gram of Ceftriaxone and 500ml/g of Metronidazole). Then marker patients from viewpoint of site of LEAK anastomosis were

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determined by using abdominal X-ray with Gastrografin, Methylene blue or sonography. From viewpoint of site of wound, in compliance with clinical examination and leaking secretions from wound with fever higher than 38.5 degree, two X-ray were taken from chest and from viewpoint of embolism according to CTA and from viewpoint of MI, cardiac enzyme and from viewpoint of UTI and in compliance with U/A and U/C were evaluated. In order to calculate volume sample, it was benefit from information of Y.Plott article (18). The surface beneath the Roc curve for Lik variable based on CRP for third day after surgery was 84%. The information was analyzed by using N CSS11 software for determining volume sample and by observing reducing 30% of respondents, it was required for 227 samples of anastomosis that was finally 198 samples were evaluated and the ability of test was regarded as 90% with error type I (0.05%).

Statistical Analysis:

Statistical analysis was performed with SPSS software version 22.0. The data was classified and reported with number. Then data was compared in different time by Wilcoxon signed-rank test. First of all, a simple descriptive statistics based on average age of persons attending at this sample was calculated for following 4 groups including: Normal, SSI, Other, LEAK and also the average age for male and female was separately calculated (table 1). Then, the quality for average age of male and female was examined with T-Test and each of 3 groups were compared with normal group for classifying and examining variables of sex, group age of cancer, Albumin, diabetes, smoking cigar and CRP and the level of CHI-2 was calculated for testing the hypothesis of independence of these groups by using 7 variables (table 1). Then the 4 subgroups for average level of CRP and WBC in different times were calculated (table 2). In next stage, whereas distributing age variables, CRP and WBC in subgroups were not normal, it was benefit from double sample Mann–Whitney test and non-parametric T-Test for average independent 2 samples for comparing distribution of these variables on normal group and each normal group was divided into other 3 subgroups. In next stage, for each time of measuring CRP and WBC, the variables of Infection, LEAK, UTI, Pneumonia were evaluated for assessing the ability of these variables for anticipating CRP and WBC variables. In order to obtain this task, an ROC curve was drawn and amount of AUC, sensitivity and property was calculated and the best amount of Cut Off for each 4 variables is calculated (table 3 and 4). Then the variable of Infection (diagram 1 and 2) Leak (diagram 3 and 4) for second and fourth measurement, variable Pneumonia

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(diagram 5 and 6), UTI (diagram 7 and 8) for fifth and sixth measurement time and Rock diagram for single shape was drawn. The reason of selecting these specific times was that in most of Rock diagrams at first stage, the maximum level of AUC was obtained. Finally, method of changing variables WBC and CRP during time is shown in 2 separate diagrams (diagram 9 and 10).

Results:

This study consisted of 189 patients with anastomosis site that were gone under elective surgery of GI system (Gastrointestinal tract). 26 patients (13.7%) showed side effect and remained 163 patients (86.2%) did not show any side effects (table 1-8), average variable of age was 56.9 years (CL= 55.3 – 58.5) and in men and women is respectively: 54.4 (51.9 – 56.9), 58.8 (56.9 – 60.8) that according to T-Test, there was significant difference between average age of men and women (P-Value = 0.006). The average age in group without side effects was 61 years and in anastomosis group was 63 years and in SSI infection in site of surgery was 57.5 and RSI was average 64 years. Among total 227 anastomosis, 73 cases were related to stomach (32.1%), 57 cases were related to small intestine (25.1%), 71 cases were related to colon 31.2% and 26 cases were related to rectum surgery (11.4%). The most common side effects of RSI with 11 cases (5.8%) and second one is anastomosis with 9 cases (4.7%) and infection in site of surgery with 6 cases (3.1%) and in sum there were 9 cases with anastomosis by having cancer; in which, 5 cases were related to rectum surgery, 2 cases were related to manual anastomosis, 3 cases were related to stapler, 1 case was related to anastomosis of stomach, 2 cases were related to manual colon, 1 case was related to Whipple procedure with anastomosis stapler. In sum among total 227 cases of anastomosis, 99 cases were performed manually, 55 cases were performed by stapler and 35 cases were performed by mixed manual stapler. According to table 1 for variables of age, sex, Albumin, diabetes and smoking cigar there is not significant difference between normal people for each 3 groups. According to table 2 there is not significant difference between variables of CRP and WBC among normal group and other 3 groups. In measurement after the surgery, the level of CRP and WBC for normal persons was less than other persons and SSI; nevertheless, for Other group its level was lower than normal group. On second, third and fourth day for WBC and on second day for CRP, there is not significant difference. Level of AUC is most of 70%,

80% and 90% is regarded as good, very good and excellent. During analysis days there was significant difference between 2 groups with and without side effects. For CRP on third day, whereas all items were reported, level of CRP on third day was higher than 136 and the level of measurement of CRP for all persons on third day was lower than 136. Thus, CRP on third day was able to completely anticipate and the level of AUC was 5% with sensitivity of 100 (table 3). For drawing double ROC diagrams for each of the variables, level of infection on second and fourth day (diagrams 1, 2, 3, 4) for 2 variables of Pneumonia and UTI on fifth and sixth day was observed and showed maximum level of AUC on these days (diagrams 8, 7, 6, 8-5).

Discussion

It is very important for diagnosing anastomosis for preventing from mortality and morbidity. It is required for a dependable and quick method for early diagnosis of side effects; thus, patients may be discharged from hospital in full healthy condition and preventing from causing aforesaid side effects. Serum markers may prepare information for inflammation process in human body. CRP is among acute phase protein that is created in liver and producing this protein is stimulated by cytokine(7,10). According to the Buunen study, the level of CRP as 145mg/lit on 4th day after rectum and colon surgery shows the maximum sensitivity and specialty for prevention of infectious side effects(12). According to the study of Korner, the level of CRP on third day after surgery when its level is 190mg/lit, shows the maximum sensitivity and specialty for anticipating side effects(17). According to study of Ortega, patients that level of their CRP on third day is higher than 135, shall not be discharged from hospital(19). Study of Adamina in the year 2014 for Laparoscopic colorectal surgery, showed that average CRP with maximum sensitivity and specialty for creating infectious side effects on 6th day after surgery, was 56mg/lit with sensitivity of 32% and specialty of 46% (20). In the study of Welsch, 48 patients with similar infectious side effects were separated and 48 patients without infectious side effects who performed rectum cancer surgery were separated and it showed that increasing level of CRP on third day after surgery was associated with infectious side effects i.e. Cut Off 140mg/lit (9). In the study of Mackay 160 patients having colorectal cancer surgery showed that increasing level of Cut Off on 4th day with level of 145 mg/lit with accompanies with infectious side effects (15). The study of Warschkow on 1187 patients gone under colorectal cancer resection, the level of

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CRP higher than 123 on 4th day increased ambiguity for increasing inflammation side effects (21).

In our present study, level of CRP serum with Cut Off 136mg/lit and AUC = 0.5 and sensitivity of 100% is able to anticipate LEAK anastomosis and level of CRP on 4th day of surgery, showed maximum sensitivity (100%) and specialty (96%) for anticipating LEAK anastomosis. Level of WBC on third day showed Cut Off 9.8 and Auc= 0.99 and sensitivity of 100% and specialty of 93% LEAK anastomosis. Results of present study showed that CRP is able to anticipate infectious side effects of LEAK anastomosis before emergence of clinical symptoms. Results of current and previous studies revealed that, the threshold of CRP is not equal; but, it is similar. The difference may be due to number of patients or difference in threshold for diagnosing infectious side effects having standardization problem or technique of anastomosis for surgery may be performed manually by using stapler, type of selected patients may influence on results so that in several studies only the site surgery of colon and rectum was examined; meanwhile, in the present study the entire patients gone under GI surgery and anastomosis were examined. In some of the studies it is mentioned that entire selected patients have cancer (14,16); nevertheless, in the present study the entire patients with and without cancer were examined. Moreover, type of performing surgery i.e. laparoscopy or open surgery may be effective on results of study and in some studies the emergency surgery was considered that may be effective on increasing level of CRP, in some surgical studies, it was benefit from elective surgery and also having low level of Albumin before surgery was among effective factors on level of LEAK anastomosis, some studies were performed without amending level of Albumin and under emergency condition(15,22, 23,24); meanwhile, in our study the elective surgery with amending level of Albumin was performed. The similar point in our study with other studies was increasing level of CRP and WBC by having LEAK or infection in site of surgery and level of this variable in our study is similar to other studies and for RSI group, there is lower sensitivity that maybe due to side effects of RSI out of time domain of our measurement. The present study showed that measuring level of CRP on third day after surgery may be able to anticipate LEAK anastomosis after surgery. CRP while assessing level of WBC on third day is regarded as index for discharging or lack of discharging patient from hospital and if level of CRP is higher than 136mg/lit, it is necessary for performing more studies for determining infectious side effects

including: anastomosis on patient for reducing level of mortality and morbidity and also economizing costs of patient and hospital.

Conclusion:

According to the results of current study, through controlling WBC and CRP in elective surgery of Gastrointestinal tract, it is possible to anticipate infectious side effects after surgery and also through performing early treatment, the costs of patient and hospital during hospitalization is reduced and also level of mortality and morbidity is reduced and this may be regarded as effective criterion for discharging patient from hospital.

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Table 1: Descriptive statistics for 4 groups based on variables

Variable	Normal n=164	Leak n=9		SSI n=6		Other n=11	
	Value	Value	p-value	Value	p-value	Value	p-value
Age, median(range)	61 (18-84)	63 (43-69)	0.542	57.5 (44-62)	0.400	64 (39-70)	0.522
Age (<60 / 60-69 / 70+)	79 / 73 / 12	4 / 5 / 0	0.866	4 / 2 / 0	0.798	5 / 4 /2	0.377
Sex (Female / Male)	72 / 92	3 / 6	0.733	3 / 3	1.000	4 / 7	0.758
Cancer (No / Yes)	46 / 118	0 / 9	0.115	5 / 1	0.010	4 / 7	0.512
Albumin (<3.5 / >3.5)	7 / 157	1 / 8	0.354	0 / 6	1.000	0 / 11	1.000
Diabetes (No / Yes)	107 /57	6 / 3	1.000	3 / 3	0.667	6 / 5	0.523
Smoking (No / Yes)	147 / 17	9 / 0	0.602	6 / 0	1.000	9 / 2	0.340
Preoperative white cell count, median(range)	6.9 (3.6-10.2)	6.8 (4-7.3)	0.768	6.8 (4-7.8)	0.585	7 (6-9)	0.181
Preoperative CRP, median(range)	6 (3-63)	6 (3-34)	0.294	21.5 (4-49)	0.207	11 (4-44)	0.631
Preoperative CRP (<=10 / >10)	100 /64	8 / 1	0.156	3 / 3	0.681	5 / 6	0.351

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Table 2- Difference for repeated measurement of CRP and WBC in 4 groups of study

Variable	Normal n=164 Median(range)	Leak n=9 Median(range)	p-value	SSI n=6 Median(range)	p-value	Other n=11 Median(range)	p-value
Preoperative CRP	6 (3-63)	6 (3-34)	0.294	21.5 (4-49)	0.207	11 (4-44)	0.631
Day 1	67 (14-111)	103 (76-135)	0.000	86.5 (67-117)	0.013	84 (62-94)	0.018
Day 2	56.5 (7.6-111)	127 (102-168)	0.000	102.5 (97-117)	0.000	74 (52-111)	0.103
Day 3	54 (12-112)	148 (136-168)	0.000	111.5 (84-16)	0.000	80 (38-96)	0.003
Day 4	44 (14-102)	115 (94-133)	0.000	91.5 (62-167)	0.000	76 (44-117)	0.000
Day 5	36 (12-198)	98 (76-136)	0.000	78.5 (54-120)	0.000	84 (28-104)	0.000
Day 6	28 (10-80)	94 (46-115)	0.000	100 (22-122)	0.002	96 (10-108)	0.000
Preoperative WBC	6.9 (3.6-10.2)	6.8 (4-7.3)	0.768	6.8 (4-7.8)	0.585	7 (6-9)	0.181
Day 1	8.0 (4.7-11.6)	9.8 (8-13.1)	0.001	10.3 (7.8-11.2)	0.006	9.1 (7.1-10.2)	0.152
Day 2	8.3 (4.8-11.2)	10.7 (9.2-14)	0.000	9.8 (8.4-12.8)	0.003	8.4 (7.4-9.8)	0.384
Day 3	8.0 (3.1-11.3)	12.3 (9.8-15.3)	0.000	10.1 (8.1-14.9)	0.003	8.1 (7-10.8)	0.306
Day 4	7.6 (5.1-11.1)	11.1 (8.2-14.8)	0.000	9.2 (8.4-12.8)	0.000	7.9 (7-9.4)	0.123
Day 5	7.4 (4.1-10.3)	9.4 (8.4-13.9)	0.000	8.8 (8.1-12.9)	0.001	8.7 (6.4-10.8)	0.001
Day 6	7.1 (4.0-10.4)	8.9 (7.4-13.6)	0.000	9.5 (7.1-11.2)	0.011	9.6 (6.2-12.3)	0.001

Table 3- Relationship between repeated measurement of CRP and WBC with Leak and Infection variables

Variable	Leak				Infection			
	AUC	Cut-Off	Sensitivity	Specificity	AUC	Cut-Off	Sensitivity	Specificity
Preoperative CRP	0.61	8	0.89	0.43	0.64	36	0.43	0.96
Day 1	0.90	87	0.89	0.80	0.80	80	0.86	0.66
Day 2	0.99	102	1	0.94	0.96	97	1	0.93
Day 3	0.50	136	1	0	0.94	84	1	0.84
Day 4	0.98	94	1	0.96	0.91	82	0.86	0.87
Day 5	0.95	76	1	0.85	0.88	54	1	0.68
Day 6	0.92	87	0.89	0.92	0.85	64	0.86	0.80
Preoperative WBC	0.52	6.2	0.89	0.34	0.53	7.2	0.43	0.77
Day 1	0.81	9.4	0.67	0.82	0.84	10.1	0.71	0.88
Day 2	0.94	9.2	1	0.77	0.86	9.1	0.86	0.73
Day 3	0.99	9.8	1	0.93	0.86	9.4	0.71	0.86
Day 4	0.95	9.4	0.89	0.95	0.91	8.4	1	0.72
Day 5	0.93	8.4	1	0.81	0.88	8.1	1	0.73
Day 6	0.87	8.1	0.89	0.80	0.80	11.2	0.57	0.98

Table 4: Relationship between repeated measurement of CRP and WBC with variables of UTI and Pneumonia

Variable	Pneumonia				UTI			
	AUC	Cut-Off	Sensitivity	Specificity	AUC	Cut-Off	Sensitivity	Specificity
Preoperative CRP	0.46	17	1	0.18	0.48	17	1	0.18
Day 1	0.70	62	1	0.37	0.75	84	1	0.71
Day 2	0.62	54	1	0.35	0.72	87	0.67	0.84
Day 3	0.69	63	0.83	0.61	0.73	94	0.67	0.88
Day 4	0.75	64	0.83	0.72	0.91	76	1	0.80
Day 5	0.77	54	0.83	0.67	0.88	80	1	0.86
Day 6	0.80	0.96	0.67	0.92	0.88	67	1	0.80
Preoperative WBC	0.63	6.2	1	0.34	0.53	6	0.67	0.70
Day 1	0.66	7.8	1	0.35	0.56	9.1	0.67	0.67
Day 2	0.58	8.2	0.83	0.39	0.43	8.7	1	0.33
Day 3	0.58	8.4	0.67	0.63	0.62	8.1	1	0.47
Day 4	0.65	8.6	0.50	0.80	0.52	7	1	0.21
Day 5	0.67	10.2	0.50	0.97	0.78	7.8	1	0.59
Day 6	0.72	9.1	0.67	0.91	0.75	9.6	0.67	0.92
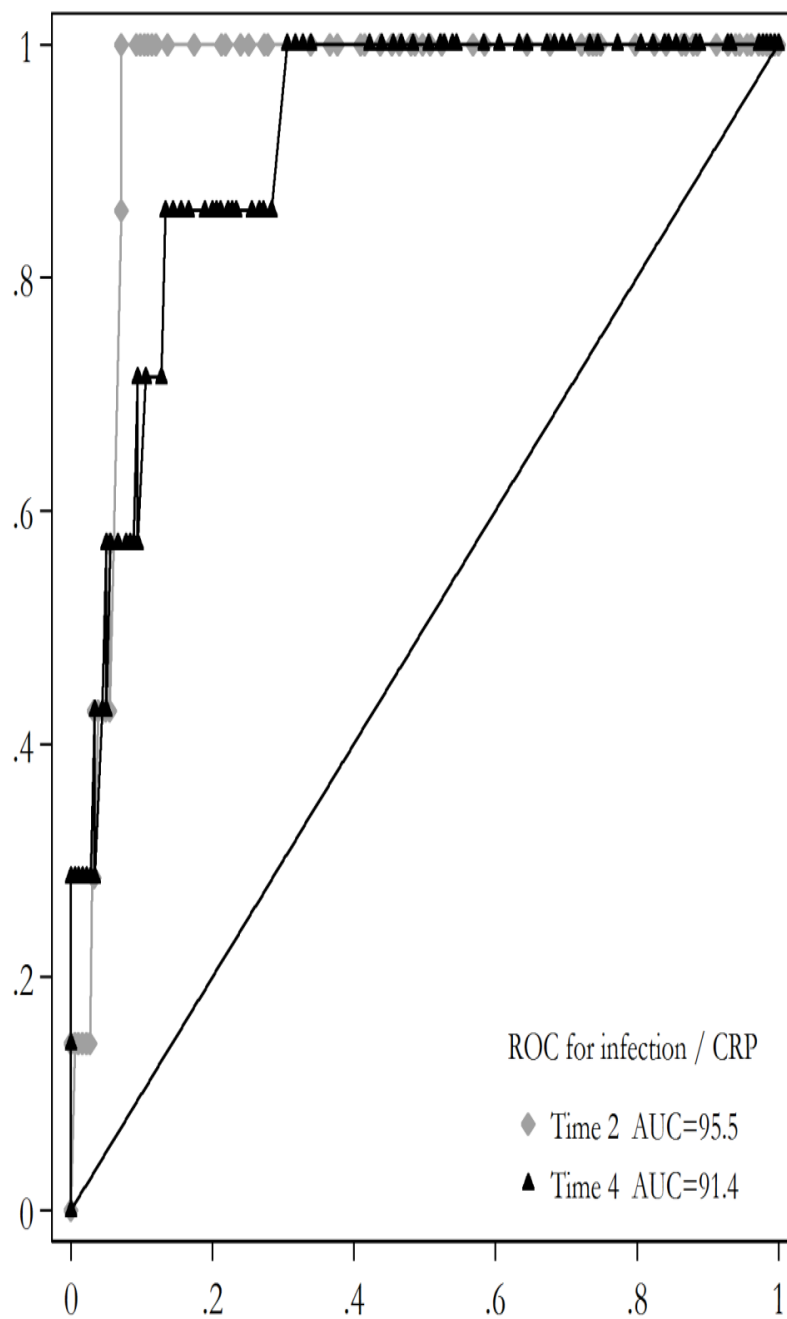
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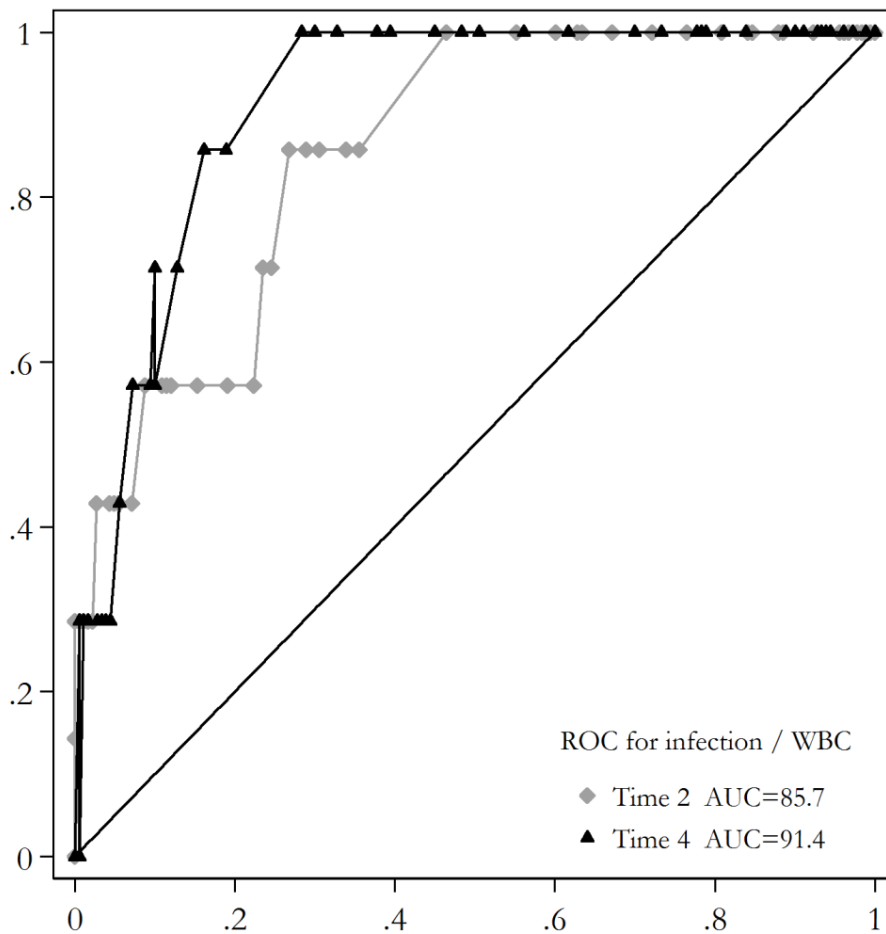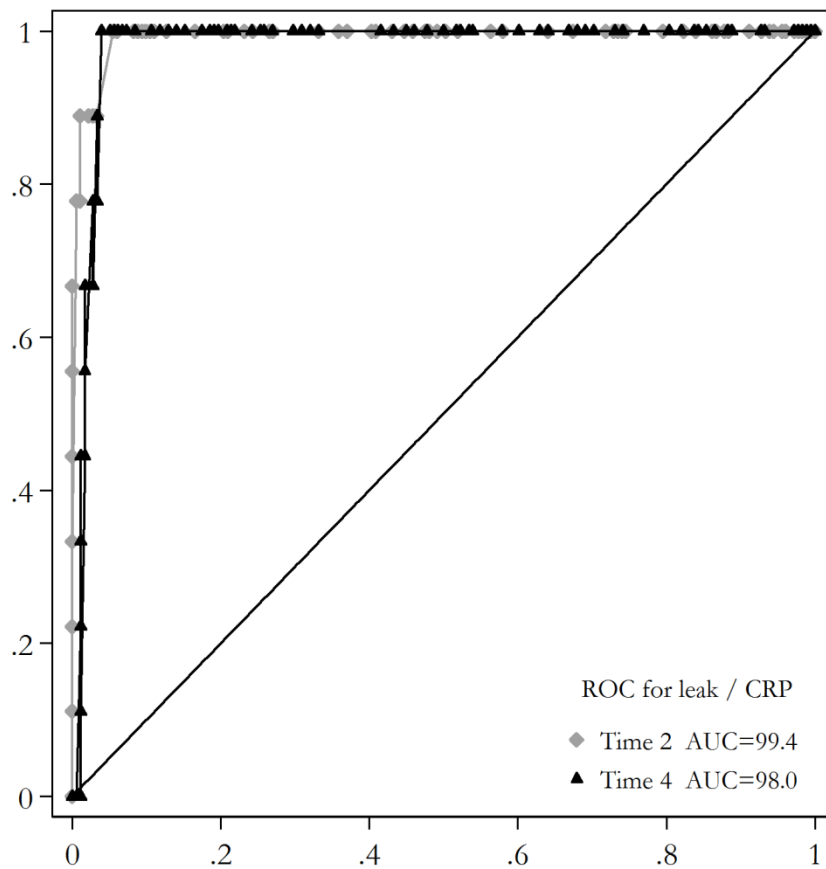
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Diagram 2-

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Diagram 3-

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Diagram 4-

Diagram 5-

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ROC for pneumonia / WBC

Time 5 AUC=66.7
Time 6 AUC=71.6

Diagram 6-

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Diagram 7-

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Diagram 8-

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Diagram 9-

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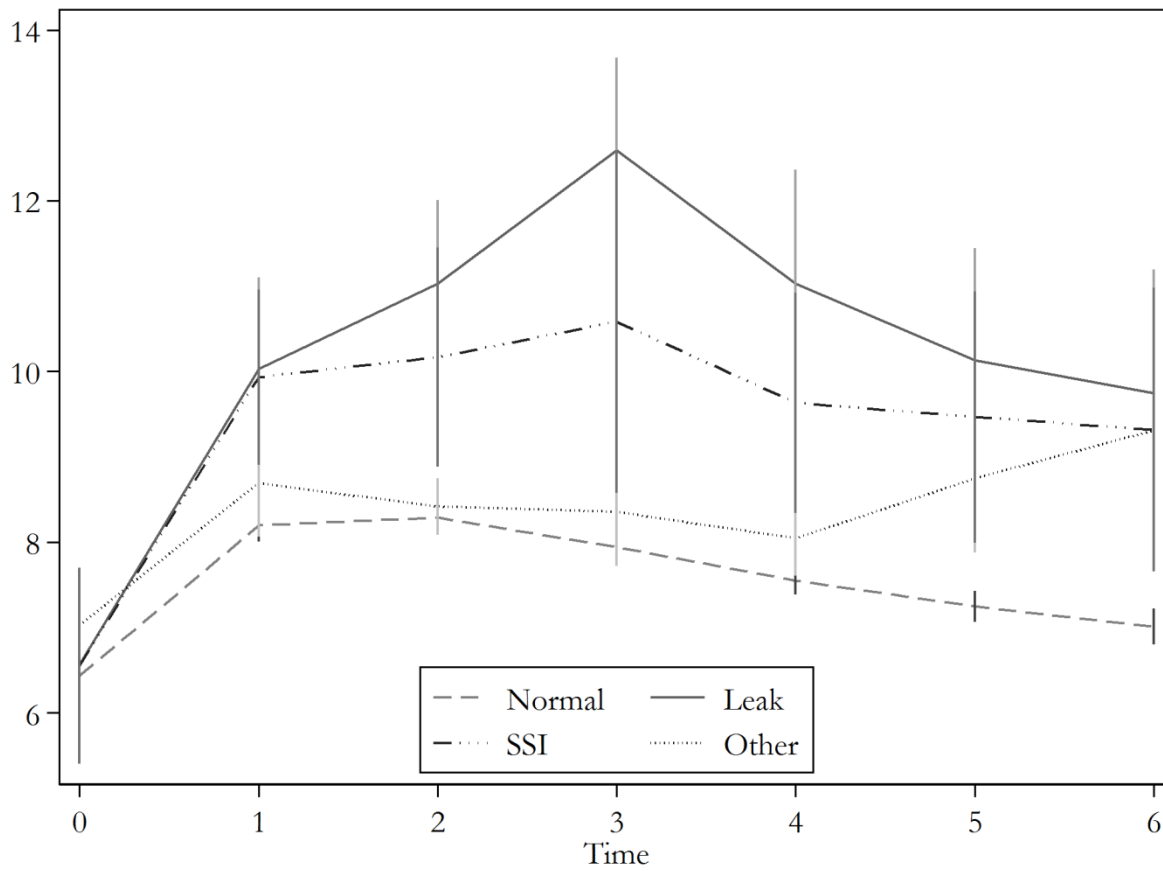
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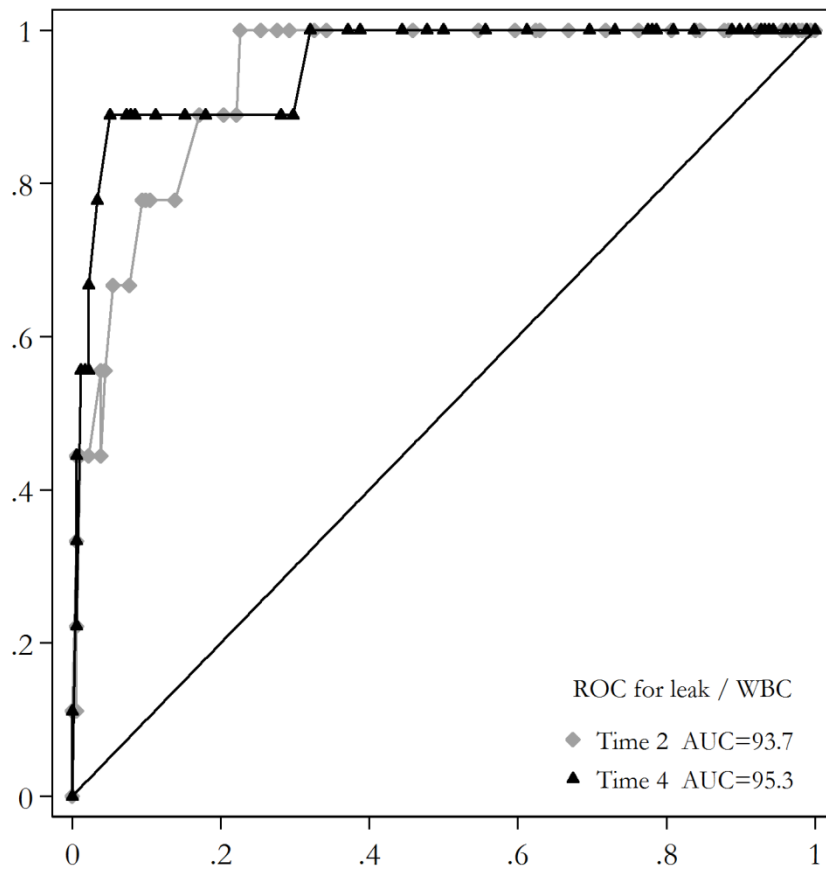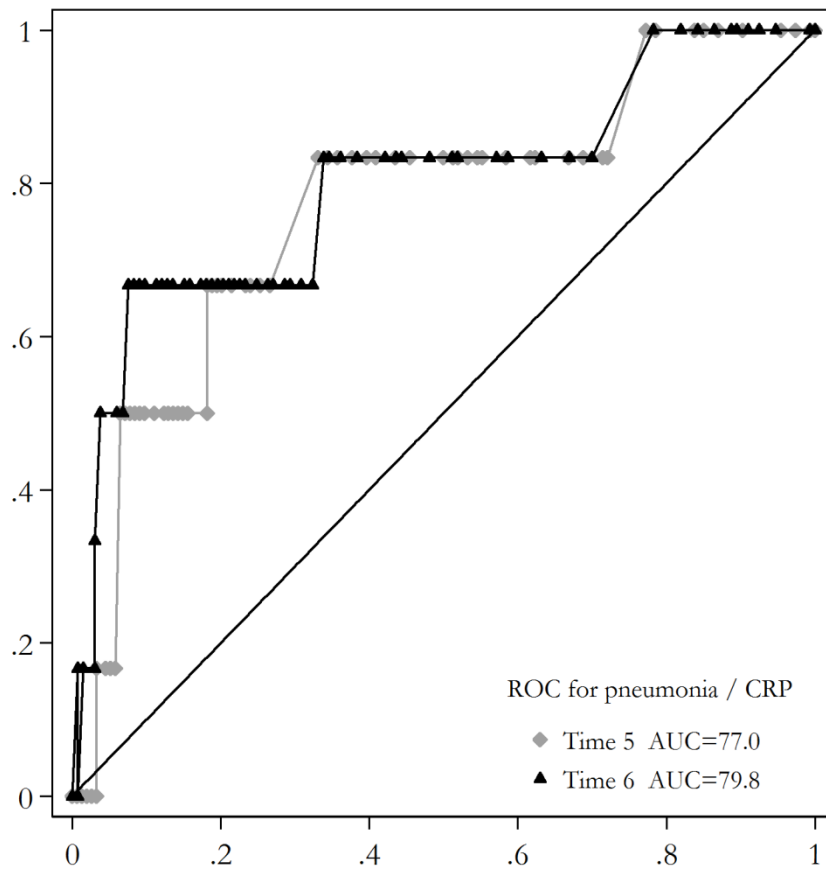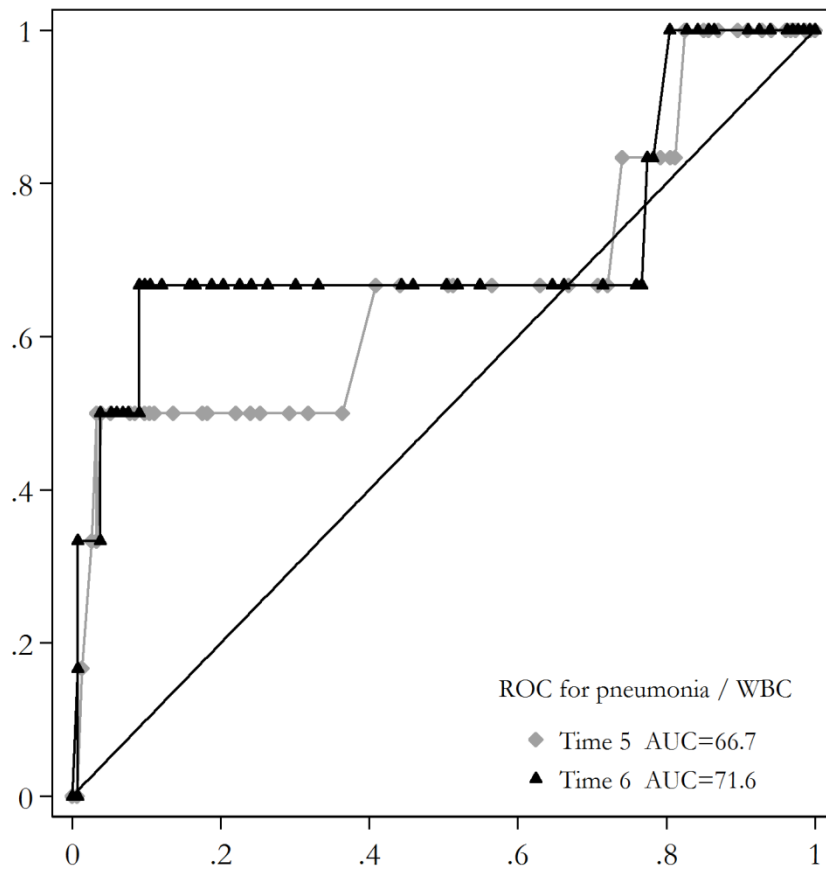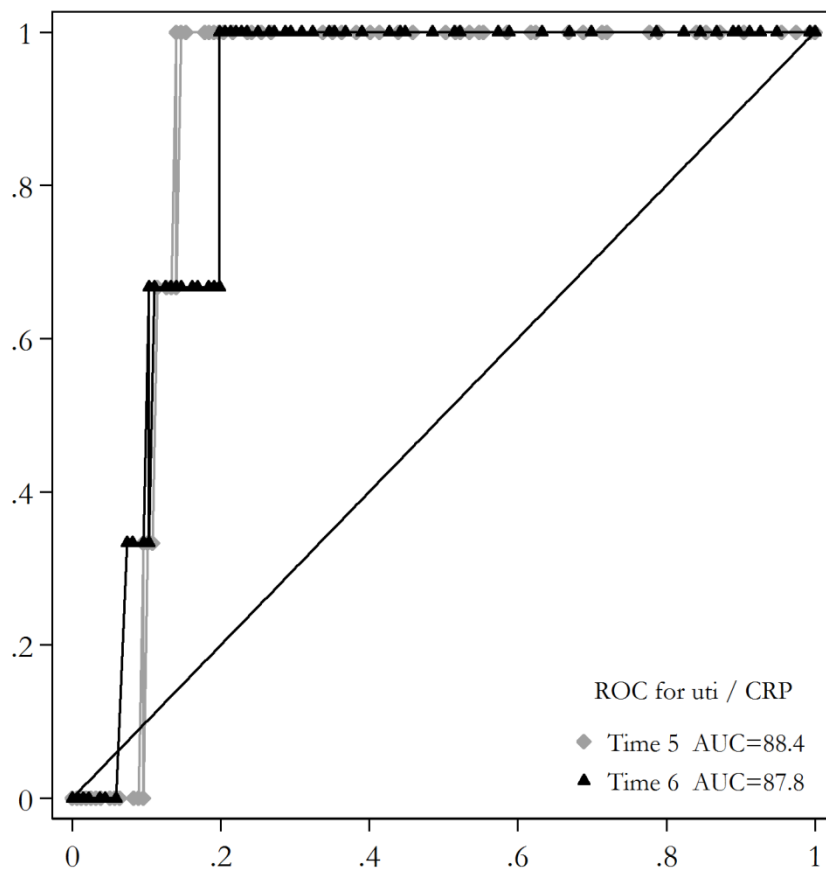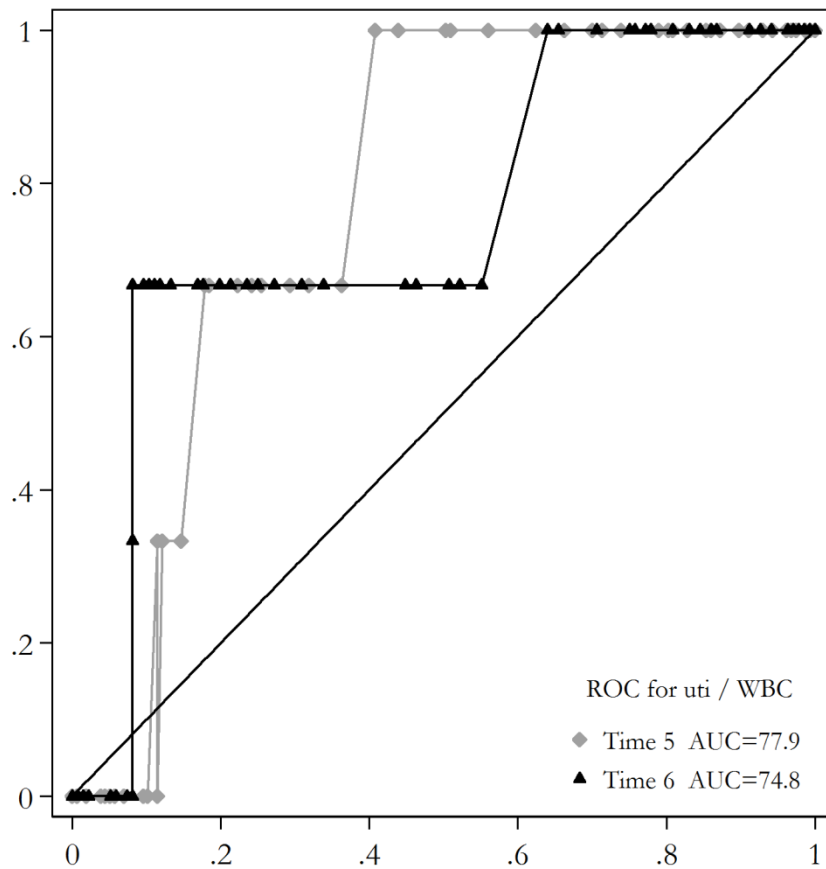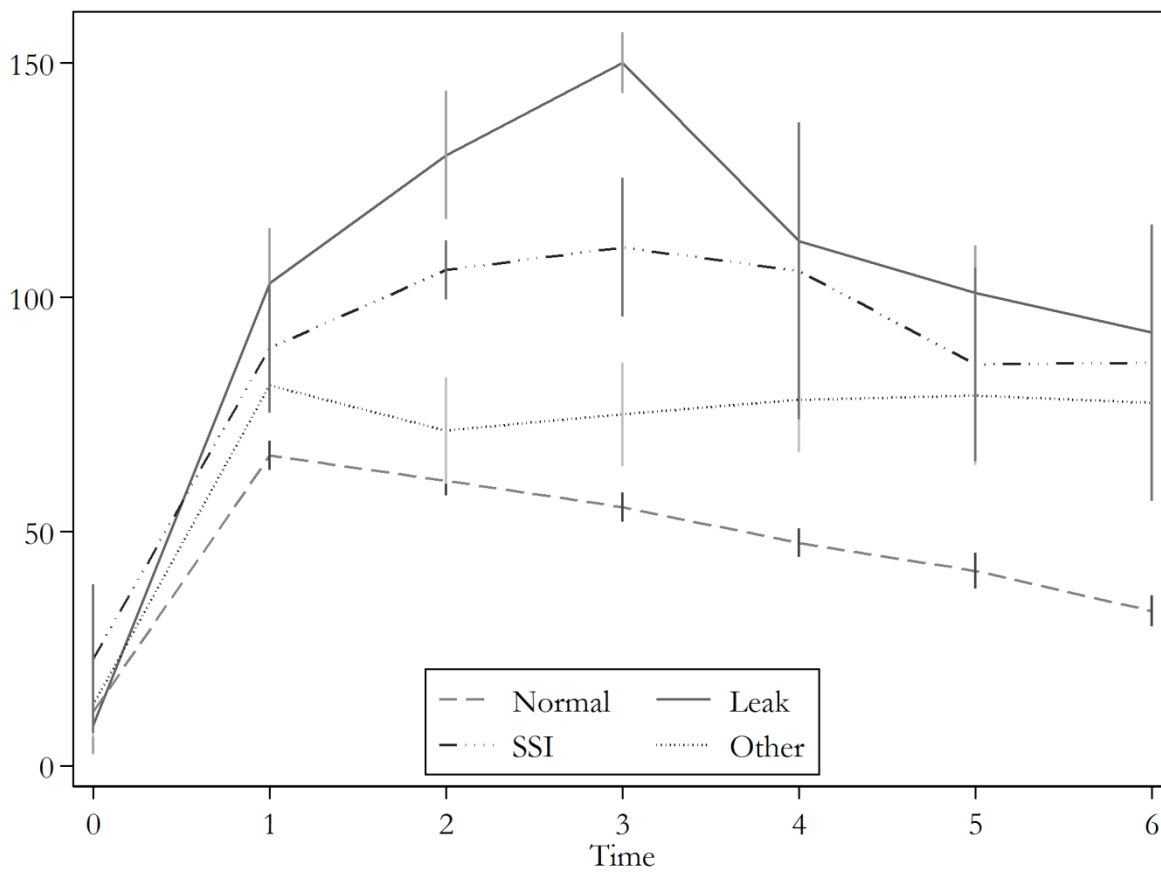
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