Total laparoscopic hemihepatectomy: outcome and learning curve in 159 consecutive patients

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ABSTRACT

Importance

Wide spread implementation of laparoscopic hemihepatectomy is currently limited by its technical difficulty, paucity of training opportunities and perceived long and harmful learning curve. Studies confirming the possibility of a short and safe learning curve for laparoscopic hemihepatectomy could potentially benefit the further implementation of the technique.

Objective

To evaluate the extent and safety of the learning curve for laparoscopic hemihepatectomy.

Design

A prospectively collected single-center database containing all laparoscopic liver resections performed in our unit between 2003-2015 was retrospectively reviewed.

Setting

Tertiary referral center, specialized in laparoscopic hepato-pancreato-biliary surgery.

Participants

Included were all patients in whom a total laparoscopic right or left hemihepatectomy procedure was started (intention-to-treat analysis), including laparoscopic extended hemihepatectomies and hemihepatectomies with additional wedge resections.

Main Outcome and Measures

Primary endpoints were clinically relevant complications (Clavien-Dindo grade ≥III). Presence of a learning curve effect was assessed with a risk adjusted cumulative sum analysis.

Results

Out of a total of 531 consecutive laparoscopic liver resections, 159 patients underwent total laparoscopic hemihepatectomy, 105 right and 54 left. In a cohort with 67 (42%) males, median age of 64 years (IQR 51-73)) and 110 (72%) resections for malignant lesions, the overall median operation time was 330 minutes (270-391) and median blood loss 500 ml (250-925). Conversion to an open procedure occurred in 17 (11%) patients. Clinically relevant complications occurred in 17 (11%) patients, with 1% mortality (death within 90 days of surgery, n=2). Comparison of outcomes over time showed non-significant decrease in conversions, blood loss, complications and hospital stay. Risk adjusted cumulative sum analysis demonstrated a learning curve of 55 laparoscopic hemihepatectomies for conversions.

Conclusions and Relevance

Total laparoscopic hemihepatectomy is a feasible and safe procedure with an acceptable learning curve for conversions. Focus should now shift to providing adequate training opportunities for centers interested in implementing this technique.

INTRODUCTION

Laparoscopic liver resection (LLR) was introduced in 1992 and numerous retrospective studies have suggested that it could reduce both postoperative morbidity and costs.(1-8) Since then, minor LLR (biopsies and small wedge excisions, left lateral sectionectomies and anterior segmentectomies) have become routine procedures and the 2008 Louisville consensus identified LLR as standard of care for left lateral sectionectomy. (9,10)

While minor LLR has become routine practice, major LLR (i.e. ≥3 liver segments) is still limited in normal clinical practice, potentially due to concerns regarding a significant learning curve effect due to the technical difficulties of the procedure. (2) The recently published recommendations from the Second International Consensus Conference in Morioka stated that major LLR is still in the exploration phase and that cautious introduction is recommended. (11) There is concern that the inherent benefits of the laparoscopic approach could be compromised due to limited visibility in the operative field or insufficient surgical expertise. Although there is literature suggesting major LLR is a feasible and safe procedure (12-19), no randomized controlled trials have been conducted and large series are scarce. More evidence of feasibility, safety and especially the learning curve are needed before further introduction of this promising technique can be promoted. (11)

This single center series provides the outcomes of a large cohort of total laparoscopic hemihepatectomies with the aim to determine the learning-curve for these procedures.

PATIENTS AND METHODS

Patients

A prospectively collected single-center database of all patients undergoing total laparoscopic liver surgery in our unit between August 2003 and March 2015 was retrospectively reviewed. Included were all patients in whom a total laparoscopic right or left hemihepatectomy procedure was started (intention-to-treat analysis), including laparoscopic extended hemihepatectomies and hemihepatectomies with additional wedge resections. All participants had given consent that anonymous data could be used for research purposes at the time of the operation. Official approval from an ethics committee was not obtained because of the retrospective design of the study.

Routine work-up consisted of bloodwork, abdominal computed tomography (CT) scans with triphasic contrast enhancement and/or liver-specific double-contrast magnetic resonance imaging (MRI). The results of these tests were discussed in a multidisciplinary meeting including liver surgeons, medical oncologists, gastroenterologists, radiologists and pathologists. The final decision regarding the surgical approach was based on the patient's performance status, resectability of the lesion, presence and extent of possible extrahepatic disease and sufficient functional parenchymal remnant.

Outcomes

Baseline characteristics included patient demographics, indication for surgery (benign/malignant), preoperative chemotherapy, ASA score, tumor size and whether multiple procedures were performed at once (e.g. hemicolectomy, splenectomy or closure of ileostomy). Cholecystectomy was not considered an additional procedures as it is part of our operative technique for hemihepatectomy.

Study endpoints included operating time, intraoperative blood loss, conversion, margin status (microscopic tumor free (R0) or microscopic tumor involvement (R1)), major postoperative complications (Clavien-Dindo ≥III; primary endpoint) (20), postoperative stay (total stay and High Dependency Unit (HDU) stay) and mortality (death within 90 days of surgery or within hospital admission). Margin status was only assessed for curative, non-debulking or non-cytoreductive resections of malignant lesions. Debulking and cytoreductive resections are R1 resections by definition and margin status in benign lesions has no clinical value.

Initially, all operations were performed by one of two surgeons (NP and MA), both with extensive experience in open liver surgery. Before starting with laparoscopic hemihepatectomies, both had performed multiple minor liver resections (19 and 17, respectively). Eighty-six percent of hemihepatectomies were performed by these two surgeons. Once proficiency with the technique was acquired, they introduced two more members of the unit (TA and AT) to the technique who then performed the other 14% of resections.

Surgical technique

Our group has previously published detailed descriptions of the technique for major laparoscopic right and left hemihepatectomy. (16,17) No hybrid techniques were used.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Windows version 21.0 (SPSS Inc., Chicago, IL, USA). Results were reported as median with interquartile range (IQR) as appropriate for continuous not normally distributed variables. The Mann-Whitney *U* test was used to compare continuous variables between groups as appropriate. Categorical variables were reported as proportions and compared between groups using chi-square test or Fisher's exact test as appropriate. A two-tailed *P*-value of <0.05 was considered statistically significant.

A subgroup analysis was performed by comparing the results of three time periods to assess a potential learning curve effect. Group A (2006, 2007 and 2008) represented the early experience with the technique. Group B (2009, 2010 and 2011) represented the further development of surgical skills and proficiency with the technique. Group C (2012, 2013 and 2014) represented the stage were proficiency with the technique was achieved and further members of the unit were introduced to the technique. To identify a disproportionate influence on outcomes by extended procedures, a sensitivity analysis was performed by excluding all extended procedures from the analysis.

RA-CUSUM

A risk-adjusted cumulative sum (RA-CUSUM) analysis is a plot of the difference between the cumulative expected outcome of a categorical variable and the actual observed outcome. A multivariable logistic regression model for conversion from laparoscopic to open hemihepatectomy was constructed using backward selection. The final model included preoperative chemotherapy, experience of surgeons and tumor size. Using this model a RA-CUSUM analysis was performed to assess the learning curve for laparoscopic hemihepatectomy. The RA-CUSUM plot provides a visual representation of the cumulative conversions of the group of surgeons, taking into account the associated risk for a particular case-mix. Every operation is plotted from left to right and the line goes up for procedures completed laparoscopically whereas the line goes down for procedures which were converted to the open approach. The magnitude by which the line ascends or descends is determined by the difference between the observed and expected proportion of conversion. For all laparascopically performed hemihepatectomies the line ascends by an amount equal to the estimated probability of conversion and for every surgery that is converted to open the line descends by an amount equal to the estimated probability of non-conversion.

The RA-CUSUM plot was constructed for all hemihepatectomies performed and as a sensitivity analysis, a plot was also constructed for right sided hemihepatectomies only. RA-CUSUM analyses were performed using R for Windows version 3.1.2 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

Of 531 consecutive LLRs performed between August 2003 and March 2015, 159 were hemihepatectomies (105 right, 54 left). This included 19 laparoscopic extended hemihepatectomies (13 right, 6 left). The first laparoscopic hemihepatectomy was our 23th LLR; 3 years after the first LLR had been performed.

The group consisted of 67 males and 92 females, with a median age of 64 (51-73) years. Of all resections, 110 (72%) were for malignant disease. Simultaneous procedures, including hemicolectomy, splenectomy, closure of ileostomy and wedge resections from surrounding structures (inferior vena cava, stomach, diaphragm) were performed in 7 (4%) cases. Twenty-nine (18%) patients needed additional wedge resections from other segments. Full patient characteristics and detailed procedure descriptions are presented in Table 1.

Perioperative results

In the majority of malignant cases (91%, n=100), a curative resection was attempted. More details on margin status of these resections can be found in Table 2. For some lesions, a curative resection was impossible due to the extent of the disease and a debulking or cyto-reductive resection was performed (9%, n=10, mostly for neuroendocrine tumors (n=7)).
Median operating time was 330 minutes (270-391) and intraoperative blood loss 500 ml (250-925). Conversion to a mini laparotomy or complete open procedure occurred in 17 (11%) procedures. The reasons for conversion included bleeding (n=7), difficulty mobilizing the liver due to dense adhesions (n=5), poor visualization of the lesions (n=3) or to ensure R0 resection (n=2). Patients stayed a median of 5 days (4-6) in hospital, of which 1 day (1-2) in the high dependency unit. A total of 29 (18%) patients experienced complications, of which 17 (11%) were Clavien-Dindo grade 3 or higher. Complications included abscess formation

(n=8), pneumothorax (n=2), bile leakage (n=2), delayed bleeding, small for size liver with ascites, intraoperative splenic injury requiring splenectomy, septic shock and cardiac arrest. Mortality was 1% with two post-operative deaths: lactate acidosis resulting in cardiac arrest and respiratory failure due to pneumonia. Perioperative results are displayed in Table 3.

Subgroup analysis

Three groups were formed based on the year of the operation. Group A (2006-2008) consisted of 27, group B (2009-2011) of 58 and Group C (2012-2014) of 74 resections. All resections in Group A and all but 3 resections in Group B were performed by the initial two surgeons NP and MA. Two additional surgeons performed their resections in Group C. Comparison of groups revealed non-significant decrease in conversions, blood loss, postoperative complications, HDU stay and hospital stay (data not shown).

Sensitivity analysis

Outcomes did not change when the extended resections were excluded from analysis.

RA-CUSUM analysis

The learning curve for conversion in laparoscopic hemihepatectomy is displayed in Figure 1. A visual inspection of the RA-CUSUM plot shows an increased conversion rate at the beginning of the series that started to decrease after 19 hemihepatectomies. This development halted for another 20-30 cases before it progressed from 55 cases onward. A second dip in the figure can be observed around 145 cases. A sensitivity analysis including only right sided hemihepatectomies showed a similar development: increasing conversion rate at the beginning, starting to decrease from18 cases but halting untill progressive decrease from 45 cases onward (Figure 2).When only left sided hemihepatectomies were included there appeared to be no learning curve at all (data not shown). In exploratory analyses, differences in patient selection in the subgroups 0-20, 20-40 and thereafter were undetectable.

Upon further examination of this cut-off of 55 patients, by comparing the outcomes of the first 55 patients to the rest, no significant differences were found in operating time, blood loss, postoperative complications and postoperative hospital stay.

DISCUSSION

This study is the first analysis of a learning curve in a large series of total laparoscopic hemihepatectomies only. With RA-CUSUM learning curve analysis a learning curve of 55 procedures for conversion was demonstrated. Based on a median operating time of 330 minutes (270-391), blood loss of 500 ml (250-925), 11% (n=17) conversions, 11% (n=17) major postoperative complications and 1% mortality, total laparoscopic hemihepatectomy was considered a safe procedure within a group of liver surgeons in a high-volume unit.

The feasibility and safety of major LLR has been suggested by several large previous studies but none of these studies focused specifically on laparoscopic hemihepatectomies. (12-15,18) Although the results from the current study are very comparable, previous studies included posterior- and tri-segmentectomies, central hepatectomies, or hand-assisted resections in their analyses. The analysis in the current study is a valuable addition to the existing literature for several reasons. First, major LLR encompasses several operations and it has been shown that a division in subcategories is appropriate to reflect differences in surgical outcomes. (21) Second, with the debate on hand-assisted vs. total laparoscopic techniques still ongoing and a lack of direct comparisons of these two techniques, separate analyses clearly have a value. Dagher *et al.* (13) found in their international multicenter study that hand-assisted operations had a shorter operation time and patients spent less time in hospital after surgery. On the other hand, it is imaginable that total laparoscopy has a cosmetic benefit over hand-assistance, but this is an outcome that is rarely objectively analyzed. Choice of technique is now mostly up to surgeon's preference and surgical expertise, with hand-assistance most frequently being used in early experiences and outside of Europe. (13,14) Lin *et al*. (15) stated in their review of three different laparoscopic approaches, including the total laparoscopic and hand-assisted techniques, that further research could help identify the unique clinical application possibilities of each technique.

Upon visual inspection of the RA-CUSUM analysis demonstrated in figure 1, no clear conclusion can be drawn at first glance and its interpretation is up for discussion. Identifying a learning curve with RA-CUSUM analysis usually entails no more than identifying the lowest point in the figure. In this case that would be at 19 procedures. However, the figure seems to hover at that point and only shoot up again after 55 cases. The possibility that this point around 55 cases is in fact the “true” learning curve cannot be excluded and is more in line with what has been reported previously. (22) The low incidence of conversion in this cohort and the lack of power in the prediction model used for analysis make interpretation of the figure very difficult, though the dip at 55 cases is clearly the most plausible as learning curve. The first dip at 19 procedures might be explained by the fact that the majority of early procedures (17/19) had been done by one of the two original surgeons and hence displays the individual learning curve of a highly experienced laparoscopic liver surgeon. We do believe this is an extraordinary number and vast experience in laparoscopic surgery and minor liver resections are of paramount importance to achieve such results. Junior teams starting with major LLR should have sufficient experience with minor LLR. The third dip, starting at 125 cases, clearly does not reach the lowest point and therefore does not display the learning curve for this procedure, but it is hard to believe that the accumulation of conversions in that time period is pure coincidence. During this period two additional surgeons were introduced to the technique as part of succession planning as one of the senior surgeons reduced his workload as he approached retirement from active surgical practice. Their individual learning curves could explain this finding. However, this introduction was handled in such a way that an experienced surgeon was always present in the operating room for guidance and ready to step in to avoid conversion. Therefore, we believe that this dip is part of the institutional learning curve, representing the stepwise implementation of the laparoscopic approach for more complex procedures, such as lesions with close proximity to the liver hilum or inferior vena cava, extended procedures and 2 stage procedures.

Apart from the interpretation of the RA-CUSUM analysis, we acknowledged the fact that when talking about a learning curve, a conclusion cannot be based on a single outcome like conversion. Variables such as blood loss and operating time should be looked at as well, although no clear definition exists of what variables exactly constitute a learning curve. The RA-CUSUM method does not allow for calculating the learning curve of continuous variables. Instead, we compared two groups based on the outcome of the RA-CUSUM analysis on conversion: 55 cases vs the rest. This comparison demonstrated no significant differences in operating time, blood loss or postoperative complications.

As one might expect, right hemihepatectomies were found to be more challenging than left hemihepatectomies, expressed in almost all outcomes analyzed: longer duration of operation, higher blood loss, more conversions and more postoperative complications. These findings can be explained by the need for more advanced mobilization of the liver. The sensitivity analysis for only right hemihepatectomies showed a similar figure as for all hemihepatectomies, with a most plausible learning curve of 45 procedures and for only left sided hemihepatectomies there appeared to be no learning curve at all. This could well be explained by the fact that in the first 20 consecutive patients only 2 left hemihepatectomies were performed.

One could theoretically advocate to start with laparoscopic left hemihepatectomy and only move to laparoscopic right hemihepatectomy once sufficient experience is obtained. However, in many centers patient volume may be insufficient for such an approach.

Despite promising results from the current and previous studies and with the advantages of minimally invasive surgery in mind, implementation of major LLR should be approached with

caution. (11) Prior to embarking on major LLR, surgeons should be trained and experienced in both open liver surgery, minimally invasive surgery and minor LLR. Liver mobilization, parenchymal dissection and hemorrhage control are all skills that can be developed during minor LLR and are crucial in the more complex major LLRs. Initial procedures should be straight forward after which a stepwise progression in complexity of procedures can follow. We showed that even with this set of skills and 3 year experience with minor LLR on board, and using the stepwise approach, results will still improve with experience. Trends were observed over the years towards reductions in conversion, blood loss, postoperative complications and HDU and total hospital stay, as was described before. (13,23) The added value of the RA-CUSUM analysis in this study is the determination of the number of resections needed to overcome the learning curve for conversions. Others can use this number as a guideline to their skill development when starting with this difficult procedure.
The introduction of the technique to additional surgeons within an experienced center is safe and can be done without compromising the outcomes or a second learning curve, providing they have similar experience with advanced gastrointestinal laparoscopic procedures and minor LLR. Introduction should primarily be under experienced supervision to smoothen the process and prevent unnecessary conversions, while gradually working towards decreasing supervision.

The study has some limitations, mainly its retrospective design, introducing the risk of selection bias. Some soft factors were mentioned, including the institutional style of the learning curve with multiple surgeons performing resections in different stages, that could have had an impact on outcomes and therefore make interpretation of the learning curve more difficult. However, the large size of the cohort and the promising results do propagate further prospective and randomized trials into the actual benefits of the laparoscopic approach to hemihepatectomies. Such a trial is currently underway in Europe (ORANGE II Plus Trial; https://clinicaltrials.gov/ct2/show/NCT01441856).

In conclusion, this study demonstrated the feasibility and safety of the laparoscopic approach to hemihepatectomy. When performed by surgeons with experience in open liver surgery, advanced laparoscopic gastrointestinal surgery and laparoscopic minor LLR the inherent benefits of the laparoscopic technique were not compromised in patients undergoing laparoscopic hemihepatectomy. A learning curve of 55 cases is achievable when these conditions are upheld.

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M Abu Hilal had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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FIGURE LEGENDS

Figure 1. A risk-adjusted cumulative sum (RA-CUSUM) analysis of conversions for the difference between the cumulative expected outcome and the actual observed outcome of 159 consecutive laparoscopic right and left hemihepatectomies. A multivariable logistic regression model for conversion from laparoscopic to open hemihepatectomy was constructed using backward selection to calculate the expected outcome. Every operation is plotted from left to right and the line goes up for laparoscopically performed surgery and down for procedures which were converted to the open approach. Visual inspection shows a learning curve of 55 procedures.

Figure 2. A risk-adjusted cumulative sum (RA-CUSUM) analysis of conversion for the difference between the cumulative expected outcome and the actual observed outcome of 105 consecutive laparoscopic right hemihepatectomies. Visual inspection demonstrated a learning curve of 45 procedures.

TABLES

Table 1. Baseline characteristics

	Overall (n=159)	**Total laparoscopic right hemihepatectomy (n=105)**	**Total laparoscopic left hemihepatectomy (n=54)**
Sex, male	67 (42)	44 (42)	23 (43)
Age, years (IQR)	64 (51-73)	64 (53-73)	65 (46-75)
Indication for surgery, malignant	110 (72)	78 (76)	32 (64)
Pre-op chemo	45 (28)	38 (36)	7 (13)
ASA score			
1	29 (18)	17 (16)	12 (22)
2	72 (45)	51 (49)	21 (39)
3	19 (12)	10 (10)	9 (17)
Tumor size, mm (IQR)	40 (25-70)	37 (25-69)	53 (27-80)
Multiple procedures	7 (4)	5 (5)	2 (4)
Additional wedge resection	29 (18)	22 (21)	7 (13)

Values in parentheses are percentages unless indicated otherwise, IQR = inter quartile range, ASA = American Association of Anesthesiology

Table 2. R0 resection percentage for all malignant pathologies, resected with curative intent

	Overall (n=104)	Total laparoscopic right hemihepatectomy (n=71)	Total laparoscopic left hemihepatectomy (n=33)
All resections	89/104 (86)	62/71 (87)	27/33 (82)
- *CRLM*	58/67 (87)	46/52 (88)	12/15 (80)
- *HCC*	9/11 (82)	4/6 (67)	5/5 (100)
- *NET*	6/9 (67)	4/5 (80)	2/4 (50)
- *Other metastases**	7/8 (88)	5/5 (100)	2/3 (67)
- *Cholangiocarcinoma*	7/7 (100)	2/2 (100)	5/5 (100)
- *GIST*	2/2 (100)	1/1 (100)	1/1 (100)

Values in parentheses are percentages, IQR = inter quartile range, CRLM = colorectal liver metastases, HCC = hepatocellular carcinoma, NET = neuroendocrine tumor, GIST = Gastrointestinal stromal tumor

*metastatic melanoma (n=7), metastatic acinar cell carcinoma (n=1)

Table 3. Perioperative results

	Overall (n=159)	Total laparoscopic right hemihepatectomy (n=105)	Total laparoscopic left hemihepatectomy (n=54)
Operation time, mins (IQR)	330 (270-391)	345 (300-415)	270 (218-345)
Intraoperative blood loss, ml (IQR)	500 (250-925)	550 (350-1150)	300 (200-638)
Conversion	17 (11)	14 (13)	3 (6)
Pringle manoeuvre	104 (65)	61 (58)	43 (80)
Total hospital stay, days (IQR)	5 (4-6)	5 (4-7)	4 (3-5)
HDU stay, days (IQR)	1 (1-2)	1 (1-2)	1 (1-1)
Postoperative complications	19 (12)	15 (14)	4 (7)
Mortality	2 (1)	2 (2)	0

Values in parentheses are percentages unless indicated otherwise, IQR = inter quartile range, HDU = High Dependency Unit

Figure 1

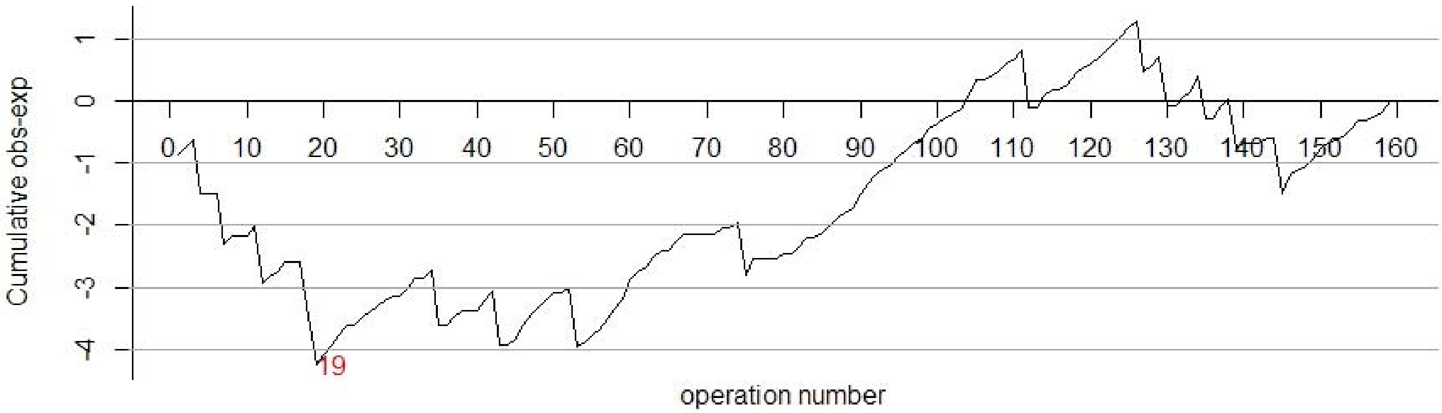
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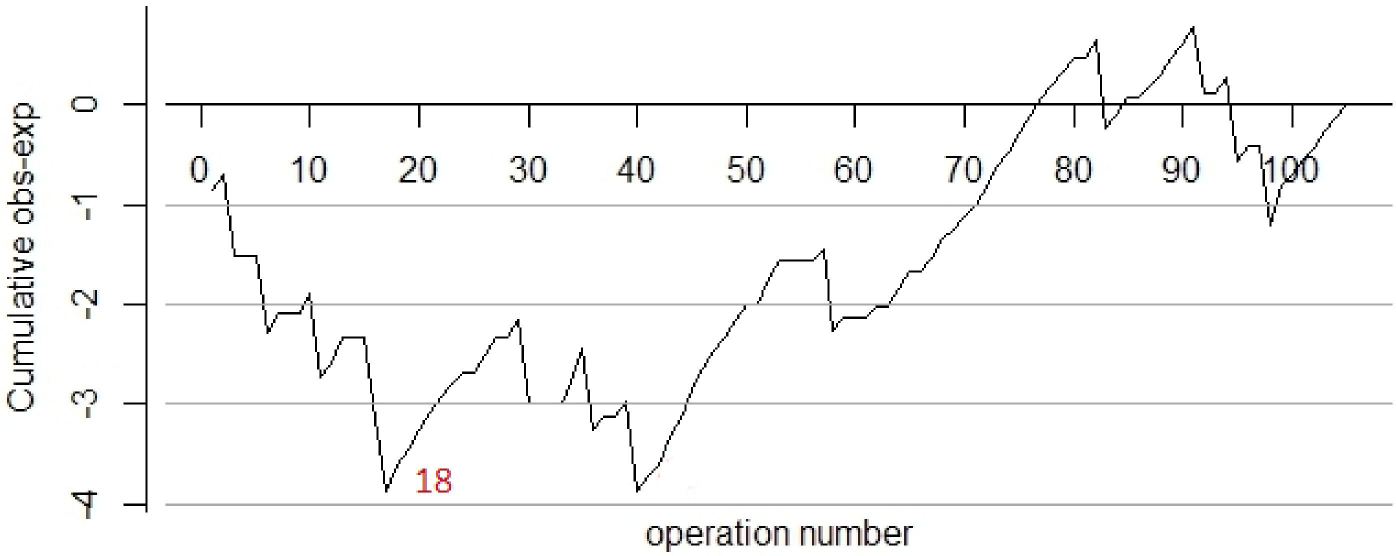
Figure 2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operation number