Peer Review File

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First external peer review

Reviewer A

Below is my peer-review report:

• General: The article concentrates on the reasons for readmissions after adrenalectomy to guide the surgeon for the best treatment options in the individual case.

• Specific:

1) Abstract

Correct

2) Introduction

Correct

3) Methods

Correct

4) Results

Do the authors have data about right and left-sided adrenalectomies? Are there any differences in readmissions between these two groups?

Response 4: The data of lateralization was not reported in the NRD database. However, using another national cancer database, we ran some analysis for this regard in another paper (unpublished), and we compared the outcomes between patients with left and right sided adrenalectomies and we found no statistical significance. Attached below the comparison between the two groups from our previous analysis.

Post-operative outcomes					
30-days mortality	Alive/censored	1101 (94.7)	1285 (95)	0.78	*Reference*
	Died	62 (5.3)	68 (5)		0.94 (0.66-1.33)
90-days mortality	Alive/censored	1051 (90.4)	1229 (90.8)	0.73	*Reference*
	Died	112 (9.6)	124 (9.2)		0.94 (0.72-1.23)
30-days readmission	Negative	1749 (96)	1921 (95)	0.12	*Reference*
	Positive	72 (4)	102 (5)		1.29 (0.95-1.76)
Postoperative LOS	Median (Quartiles)	5 (3-7)	5 (3-7)	0.98	

Undetermined cases were deleted. Stage I: T1N0M, stage II: T2N0M0, stage III: T1, T2N1M0, T3N0M0, stage IV: T3N1M0, T4N0M0, T4N1M0

Would you please explain "the technical complications"?

Response 4: Thank you for the remark. Based on this comment, we modified supplementary Table S1 to show the detailed interpretation of the ICD9 codes used. We have specified complications in depth (*See Supplementary Table S1*). The following section (below) shows the technical complications only.

9982	Accidental puncture or laceration during a procedure, not elsewhere classified
9984	Foreign body accidentally left during a procedure

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9986	Persistent postoperative fistula
9987	Acute reaction to foreign substance accidentally left during a procedure
55321	Incisional hernia without mention of obstruction or gangrene
5778	Other specified diseases of pancreas
415	Acute pulmonary heart disease
41519	Other pulmonary embolism and infarction
5061	Acute pulmonary edema due to fumes and vapors
5069	Unspecified respiratory conditions due to fumes and vapors

Do the authors have data about the rate of reoperations and their cost?

Response 4: We found 8 and 4 cases reoperation at different time points (30-days) and (90-days) and we can't report relevant data for variables counting below 10 to avoid identification of study subjects *according to the policy of HCUP*. Regarding the cost, NRD files for 'cost to charge ratio' and hospital charges were used to calculate hospital costs for each patient, as shown below:

5) Discussion
Do the authors have proposals/ideas on what may be done to lower the number of readmissions apart from organisational changes? It is impossible to change the profile of patients. What about the technical differences between the surgical methods? Are there any with lower readmissions rates?

Response 5: In discussion, we included that open procedure is associated with higher readmission rates than a laparoscopic procedure. We also discussed DVT prophylaxis and monitoring for bleeding. While we agree that patient population cannot be changed, we believe it is important to identify patients at risk of readmission so clinicians can be better prepared.
Line 188-195

6) References
Correct
7) Figures
Figure 2.
Would you please explain the shortcut CVS. Figure 2C and 2E Please correct Pulmonay to Pulmonary

Response 7: Thank you for your notes. Figure 2 was changed to a supplementary figure based on the suggestion of Reviewer B.

8) Tables

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Correct

9) Conclusions

Correct

Summary

The article is well written with high-quality statistical analysis. There are several articles on a similar topic that the authors mentioned in the discussion and references section. Still, the work adds essential data to the ongoing discussion about readmission rates after adrenalectomy.

With best regards

Reviewer

Reviewer B

Sound paper.

This is a cross-sectional analysis of readmission following adrenal surgery in the US and the cost burden for health services. There were 20,494 patients examined over 5 years. The aims of the study were to assess the risk of readmission; to identify the clinical, demographic, and administrative factors associated with readmission; and to determine the fiscal burden. Overall, the manuscript is well written with clear aims. The methodology is reproducible. Approximately, 8% of patients are readmitted after 30 days and 12.7% are readmitted after 90 days. Prolonged initial admission and post-operative complications were associated with increased risk of admission. Complications were more common amongst patients with malignancy or being treated at a low volume centre. Readmission extended overall LOS by 2days with an estimated increased cost of $18500 per person.

Major Comments

Unfortunately, large scale database data commonly lacks sufficient clinical detail required for meaningful results. Categories like 'technical' and 'renal complications' are too vague to warrant further analysis.

Response: Thank you for the remark. Based on this comment, we modified supplementary Table S1 to show the detailed interpretation of the ICD9 codes used. We have specified complications in depth (See Supplementary Table S1). The following section (below) shows the technical and renal complications, while others exist in the resubmitted version of supplementary materials.

Technical complications	9982	Accidental puncture or laceration during a procedure, not elsewhere classified
	9984	Foreign body accidentally left during a procedure
	9986	Persistent postoperative fistula
	9987	Acute reaction to foreign substance

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		accidentally left during a procedure
	55321	Incisional hernia without mention of obstruction or gangrene
	5778	Other specified diseases of pancreas
	415	Acute pulmonary heart disease
	41519	Other pulmonary embolism and infarction
	5061	Acute pulmonary edema due to fumes and vapors
	5069	Unspecified respiratory conditions due to fumes and vapors
Renal complications	5845	Acute kidney failure with lesion of tubular necrosis
	5846	Acute kidney failure with lesion of renal cortical necrosis
	5847	Acute kidney failure with lesion of renal medullary [papillary] necrosis
	5848	Acute kidney failure with other specified pathological lesion in kidney
	5849	Acute kidney failure, unspecified
	5856	End stage renal disease

Minor Comments
1. There are too many figures. F1 and F4 are relevant and should stay. F2 is complicated (delete). F3 is nice but delete if space is of concern.

Response 1: We agree that figure 2 may be complicated for some readers, so we have included it as a supplementary figure for any that may view the figure as helpful.

2. The figures look like they have been copied from another file and are blurry. I would redo these or scan a higher resolution image.

Response 2: Editable images are attached in the resubmitted version (pptx file).

3. Where is table 2?

Response 3: Thank you for pointing out this error. We have corrected the table order.

Reviewer C

This is an interesting and generally well written manuscript. The number of patients are large, which is a novelty for this relatively rare, but complex, procedure.
I have a few specific comments:-
1. I would avoid using the term 'predictor' for this observational study. 'Correlate' or

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'associated with 'is more appropriate.

Response 1: Thank you for the remark. We modified the word as suggested. (*See Lines 33 and 69*).

2. Make it clear that the setting is the United States in the abstract and in the first paragraph of the introduction. The entire manuscript focusses on US data, and this needs to be very clear for an international readership.

Response 2: We included "United States" in Abstract
Line 34

3. There is some recent data which may be relevant to the discussion on volumes and outcomes, although previous literature is generally well covered.
a) Gray WK, Day J, Briggs TWR, Wass JAH, Lansdown M. Volume-outcome relationship for adrenalectomy: analysis of an administrative dataset for the Getting It Right First Time Programme. Br J Surg 2021; 108(9): 1112-9.
b) Anderson KL, Jr., Thomas SM, Adam MA, et al. Each procedure matters: threshold for surgeon volume to minimize complications and decrease cost associated with adrenalectomy. Surgery 2018; 163(1): 157-64.
c) Simhan J, Smaldone MC, Canter DJ, et al. Trends in regionalization of adrenalectomy to higher volume surgical centers. J Urol 2012; 188(2): 377-82.

Response 3: Thank you for the suggestion. We reviewed these papers and that the information in these papers is addressed in the discussion of the resubmitted version. Lines 196 to 198, we discuss how previous literature shows that high-volume surgeons performing adrenalectomy procedures are associated with lower complication rates, shorter length of stay, and lower readmission rates.

4. The data date from 2010-14 and so to an extent are rather out of date, especially given the authors focus in the introduction section on recent increases in use of adrenalectomy and changes in practice. This is a major limitation which the authors acknowledge in the discussion section. However, they need to support the view that the results will remain consistent with current practice. I am not sure this statement is valid. I think it should be removed and the section reworded. The time period is a major limitation and I can't see any obvious mitigating factors that would mean we can be sure the findings still hold.

Response 4: Authors removed as suggested. We wished to have earlier years, but unfortunately these years (2010-2014) were available from the NRD data purchased by the corresponding author. ICD 9 codes for the years 2010-2015 three quarters and ICD10 codes for the years 2015 last quarter-2018 proved difficult to merge, but our data analyst have future plans to integrate the different variables and observations in further studies. Screening up to date literature showed articles with similar trends.

Beck et al. included data from 2011 to 2015 reported similar complications such as renal complications and bleeding. A brief report by *Alkhalili et al* analyzing data from 2011 to 2018 reported complications such as postoperative infection, sepsis, and glucocorticoid deficiency. They reported a 30-day complication rate from 7% in 2011 to 4% in 2018. Literature contains differences in sample sizes that may cause variation in complication rates. We are confident that our data conveys important information regarding complications after adrenalectomy and factors for readmission. We acknowledge that the transition to performing adrenalectomies at high volume centers and minimally invasive may lower complication rates; however, we maintain that the risk factors correlated with increased complication rate and readmission have remained constant throughout the literature. We further addressed this limitation in our discussion (lines 221 to 223).

References

- Beck AC, Goffredo P, Hassan I, et al. Risk factors for 30-day readmission after adrenalectomy. Surgery. 2018;164(4):766-773. doi:10.1016/j.surg.2018.04.041
- Alkhalili E, Kim J, Balbas J, Dodoo C, Chiba S, Ayoubieh H. Readmission Following Laparoscopic Adrenalectomy [published online ahead of print, 2021 Jun 22]. Am Surg. 2021;31348211029876. doi:10.1177/00031348211029876

5. The inclusion and exclusion criteria seem appropriate and well thought out.

6. For readmissions we need to know more about how these would be identified. Would they only be identified if they reattended the same hospital as for the index procedure? If they would not be picked up, is this a bias in favour or larger referral centres, who may take patients from out of area, but who would attend a more local hospital if any post-procedural complications occurred? Please give us further details in the methods and add as a limitation if needed.

Response 6: Patient linkage number (NRD_Visitlink) was used to identify the discharges lined to the same individual. Days to readmission were calculated from each discharge to the first rehospitalization using a coded timing variable (NRD_DaysToEvent). Patients died at primary admission, missing length of stay (LOS), or missing data to event were excluded. Because NRD data can't be tracked across years, patients discharged from January to November and January to September were screened for 30- and 90-days readmissions.
Reference:
www.hcup-us.ahrq.gov/reports/methods/2017-01.pdf

```
Title "2 : 30-day All-Cause Readmission Events" ;
/* Select all readmissions within 30 days */
proc sql ;
    create table readmissionsAll as
    select i.HOSP_NRD as HOSP_NRD_Index
        , i.KEY_NRD as KEY_NRD_Index
        , r.*
    from nrd_2014_indexEvents i                  /* Index Events   */
        inner join ReadmCandidates r             /* Readmissions   */
            on i.NRD_VISITLINK = r.NRD_VISITLINK /* Link patients  */
            and i.KEY_NRD ne r.KEY_NRD           /* Not a self join */
            and r.NRD_DAYSTOEVENT - ( i.NRD_DAYSTOEVENT + i.LOS )
                between 0 and 30
            and i.indexEvent = 1
    order by i.HOSP_NRD, i.KEY_NRD, r.NRD_DAYSTOEVENT;  /* Sort by date   */
quit ;


/* Identify closest readmission if there are multiple readmission events */
data readmissionsClosest;
    set readmissionsAll ( rename=(HOSP_NRD=HOSP_NRD_Readmit
                                  HOSP_NRD_Index=HOSP_NRD
                                  KEY_NRD = KEY_NRD_Readmit
                                  KEY_NRD_Index=KEY_NRD)) ;
    by HOSP_NRD KEY_NRD ;
    if first.KEY_NRD ;
run;


/* Merge readmissions and index events */
data readmissions_sql ;
    merge nrd_2014_indexEvents ( drop=DXCCS1 PRCCS: )
          readmissionsClosest ( in=inR
                                rename=( NRD_DAYSTOEVENT=DaysToReadmission )
                                drop=NRD_VisitLink KEY_NRD_Readmit ) ;
    by HOSP_NRD KEY_NRD ;
    attrib Readmit length = 3 label='Readmission within 30 days (0/1)' ;
    Readmit = inR ;
    label DaysToReadmission = 'Readmission date';
run ;
```

Recall of readmission events is not influenced by particular characteristics of the hospitals. We do have readmissions from small and large centers as shown in Table 1 which demonstrates the characteristics of the patient at index hospital.

Hospital Bed Size	Small	8.6
	Medium	17.9
	Large	73.4
Hospital Teaching Status	Metropolitan Teaching	23.2
	Metropolitan non-teaching	73.2
	Non-Metropolitan	3.7
Hospital volume	Low	32.3
	Medium	44.7
	High	22.6
Hospital ownership	Government Non-federal	13.8
	Private Not-for-Profit	78.8
	Private Investor Owned	7.5
Urban-rural designation	Large metropolitan areas	61.6
	Small metropolitan	34.8

	Micropolitan areas	3.3
	Non-core	0.3
Discharge disposition	Routine	91.5
	Transfers	2.6
	Home Health Care	5.7

We also would like to note that assessed outcomes of postoperative complications was performed at the time at the index hospitalization to help identify predictors of complications and readmissions prior to the occurrence of events in clinical domain, while reasons of readmissions were assessed in the data at post readmission phase.

We added details in the methodology section (lines 80-82) as suggested and added the limitation of studying more than one year of the NRD: MRD cannot be combined across data years to create a multi-year database. The patient linkage numbers do not track the same person across years. Each year of the NRD must be considered as a separate sample. (Lines 221 to 223)

7. Figures 2 and 3 are rather busy and some of the information is of only peripheral interest. It would be best to focus on key outputs, which are the model outputs. Figure 2A and 3A convey little useful information. Figures 2B, 2C and 2E and 3B might be better as a table. In any event these figures, if they are to be retained need to have appropriate legends to define the various abbreviations used.
Response 7: We created figure 2 as a supplementary figure based on the suggestion of reviewer B.

8. The discussion section seems appropriate, although a limitation should be added regarding recording of readmissions to hospitals other than the index procedure hospital, as mentioned above. The discussion on high/low volume and metropolitan/teaching hospitals will need to be adapted if this is a limitation, as validity of this as a discussion point hinges on whether the recording or readmission is complete and unbiased.
Response 8: Information on 30- and 90-days readmission could be captured for each patient even if the readmission hospital is different form the index procedure hospital. We removed last month for 30-days readmission and last 3 months for 90-days readmission to have enough time to capture readmission events within each calendar year. Hospital volume and type of hospital is ready made variables in the database and are well reported without missing.

Reviewer C

The authors have addressed most of my concerns particularly around the ability to follow up patients across different hospitals. The points raised by all the reviewers have been well considered in the response to reviewers, but the changes to the manuscript appear to be very limited and do not really address the concerns raised (and answered by the authors in the response to reviewers). In particular, the discussion points mentioned by the authors in the response to reviewers on volume outcome relationships (Gray, Anderson) and on more recent data on readmission rates (Beck, Alkhalili), surely merits more discussion than a single short sentence. It would be useful to see the discussion presented in the reply to reviewers appear in the manuscript itself and the appropriate works be cited.

We agree with reviewer C in that expansion was necessary on these points. We have include more information in lines 191 and 203 and added citations from Gray and Anderson to solidify our discussion on volume-outcomes relationship and complication rates.