Journal Pre-proof

Metabolic syndrome predicts worse perioperative outcomes in patients treated with partial nephrectomy for renal cell carcinoma

Stefano Luzzago , Carlotta Palumbo , Giuseppe Rosiello , Angela Pecoraro , Marina Deuker , Franziska Stolzenbach , Francesco Alessandro Mistretta , Zhe Tian , Gennaro Musi , Emanuele Montanari , Shahrokh F. Shariat , Fred Saad , Alberto Briganti , Ottavio de Cobelli , Pierre I. Karakiewicz

PII: S0090-4295(20)30255-7
DOI: https://doi.org/10.1016/j.urology.2020.02.019
Reference: URL 22008

To appear in: *Urology*

Received date: 7 November 2019
Revised date: 25 January 2020
Accepted date: 22 February 2020

Please cite this article as: Stefano Luzzago , Carlotta Palumbo , Giuseppe Rosiello , Angela Pecoraro , Marina Deuker , Franziska Stolzenbach , Francesco Alessandro Mistretta , Zhe Tian , Gennaro Musi , Emanuele Montanari , Shahrokh F. Shariat , Fred Saad , Alberto Briganti , Ottavio de Cobelli , Pierre I. Karakiewicz , Metabolic syndrome predicts worse perioperative outcomes in patients treated with partial nephrectomy for renal cell carcinoma, *Urology* (2020), doi: https://doi.org/10.1016/j.urology.2020.02.019

Metabolic syndrome predicts worse perioperative outcomes in patients treated with partial nephrectomy for renal cell carcinoma

Stefano Luzzago[a,b], Carlotta Palumbo[a,c] Giuseppe Rosiello[a,d], Angela Pecoraro[a,e], Marina Deuker[a,f], Franziska Stolzenbach[a,g], Francesco Alessandro Mistretta[a,b], Zhe Tian[a], Gennaro Musi[b], Emanuele Montanari[h], Shahrokh F. Shariat[i,l,m,n,o], Fred Saad[a], Alberto Briganti[d], Ottavio de Cobelli[b,p], Pierre I. Karakiewicz[a]

[a]Cancer Prognostics and Health Outcomes Unit, Division of Urology, University of Montreal Health Center, Montreal, Quebec, Canada

[b]Department of Urology, European Institute of Oncology, IRCCS, Milan, Italy

[c]Urology Unit, ASST Spedali Civili of Brescia. Department of Medical and Surgical Specialties, Radiological Science and Public Health, University of Brescia, Italy

[d]Department of Urology and Division of Experimental Oncology, URI, Urological Research Institute, IRCCS San Raffaele Scientific Institute, Milan, Italy

[e]Department of Urology, San Luigi Gonzaga Hospital, University of Turin, Turin, Italy

[f]Department of Urology, University Hospital Frankfurt, Frankfurt am Main, Germany

[g]Martini Klinik, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[h]Department of Urology, IRCCS Fondazione Ca' Granda-Ospedale Maggiore Policlinico, University of Milan, Milan, Italy

[i]Department of Urology, Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria

[l]Departments of Urology, Weill Cornell Medical College, New York, New York, USA

[m]Department of Urology, University of Texas Southwestern, Dallas, Texas, USA

[n]Department of Urology, Second Faculty of Medicine, Charles University, Prag, Czech Republicm

[o]Institute for Urology and Reproductive Health, I.M. Sechenov First Moscow State Medical University, Moscow, Russia

[p]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy

Corresponding author:
Stefano Luzzago, MD
Department of Urology, European Institute of Oncology, IRCCS, Milan, Italy
Via Giuseppe Ripamonti, 435
20141 Milan, Italy
Tel: +39 33354249298
E-mail: stefanoluzzago@gmail.com

Word count (abstract): 250
Word count (manuscript): 2556

Declarations of interest: None

Keywords: Altered fasting glucose; High blood pressure; High triglycerides; Metabolic syndrome; Obesity; Partial Nephrectomy

Research support and financial conflicts of interest: None

Acknowledgements: None

Abstract

Objectives

To test the association between metabolic syndrome (MetS) and its components (high blood pressure, BMI≥30, altered fasting glucose, low HDL cholesterol and high triglycerides) on perioperative outcomes after partial nephrectomy (PN).

Methods

Within the NIS database (2000-2015) we identified all PN patients. First, temporal trends of MetS were reported. Second, the effect of MetS components was tested in multivariable logistic regression models predicting overall and specific perioperative complications. Third, we tested for dose-response from the concomitant effect of multiple MetS components. All models were weighted and adjusted for clustering, as well as all available patient and hospital characteristics.

Results

Of 25,875 patients:1)59.3% had high blood pressure, 2)14.7% had BMI≥30, 3)21.7% had altered fasting glucose, 4)20.2% had high triglycerides and 5)<0.01% had low HDL cholesterol. One vs. two vs. three vs. four MetS components were recorded in 34.9% vs. 22.9% vs. 8.9% vs. 2.2% patients. Of all, 11.1% exhibited ≥3 components and qualified for MetS. The rates of MetS increased over time (EAPC:+12.0%;p<0.001). The four tested MetS components (high blood pressure, BMI≥30, altered fasting glucose and high triglycerides) achieved independent predictor status in multivariable models predicting overall, cardiac, miscellaneous medical, vascular and respiratory complications, as well as transfusions. Moreover, a statistically significant dose-response was confirmed for the same endpoints.

Conclusion

MetS and its components consistently and strongly predict perioperative complications after PN. Moreover, the strength of the effect was directly proportional to the number of MetS components exhibited by each individual patient, even if formal MetS diagnosis of ≥3 components has not been met.

List of abbreviations

MetS: Metabolic syndrome

HDL: high-density lipoprotein

RCC: renal cell carcinoma

PN: partial nephrectomy

BMI: body mass index

NIS: National Inpatient Sample database

EAPC: Estimated annual percentage changes

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

CCI: Charlson Comorbidity Index

OR: Odds Ratio

CI: confidence interval

NHANES: National Health and Nutrition Examination Survey

1. Introduction

Metabolic syndrome (MetS) is a cluster of risk factors for cardiovascular disease, which occur together more often than by chance alone [1]. These risk factors include: high blood pressure, altered fasting glucose, obesity, high triglycerides and low high-density lipoprotein (HDL) cholesterol. It is estimated that approximately 35% of North American population is affected by MetS [2]. Moreover, MetS is associated with aggressive pathological features of renal cell carcinoma (RCC) [3,4]. However, there are no robust data to indicate whether or not MetS predicts early adverse outcomes after partial nephrectomy (PN) [5–9]. Nonetheless, several previous reports examined the effect of individual MetS components, namely either obesity [10–18] or hypertension [19–21] or diabetes [21–25], on perioperative outcomes after PN, without adjusting for possible combined effect of other MetS components. Moreover, none of previous studies addressed the possible synergistic effect of multiple MetS components on perioperative complications after PN. To address these limitations, we tested the effect of MetS on overall and specific complications, in PN treated patients.

2. Materials and methods

2.1 Study population

We relied on the National Inpatient Sample (NIS) database (2000-2015) [26] that is composed of longitudinal hospital inpatient databases from the Healthcare Cost and Utilization Project and includes 20% of United States inpatient hospitalizations. We focused on patients aged≥18 years with primary diagnosis of RCC (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 1890), treated with PN (primary procedure ICD-9-CM code 55.4). Secondary procedure codes were used to identify lymph node dissection (ICD-9-CM codes 40.3/40.5), as well as open, laparoscopic or robotic approach (ICD-9-CM codes 17.4, 54.21 or 17.42).

2.2 Outcomes of interest

We focused on overall and specific perioperative complications. Overall complications were defined using secondary ICD-9-CM diagnostic codes and represented the sum of intraoperative and all postoperative complications (cardiac, respiratory, vascular, wound, genitourinary, gastrointestinal, infectious, transfusions, miscellaneous medical and miscellaneous surgical). Specifically, the outcome transfusion refers to the need of patients to receive blood products.

2.3 Variables definition

MetS was defined according to the International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute [1]. Specifically, MetS definition was based on having at least three out of five MetS components, namely: 1) high blood pressure, 2) BMI≥30, 3) altered fasting glucose, 4) high triglycerides and 5) low HDL cholesterol (Supplementary table 1) [27,28]. Covariables consisted of: age, gender, ethnicity (Caucasian, African-American and Others), year of surgery, surgical approach (open vs. laparoscopic/robotic), lymph node dissection, income and insurance status (private, Medicare, Medicaid, other), hospital region

(Northeast, Midwest, South, West), hospital teaching vs. non-teaching status, hospital bed size (small, medium, large) and hospital annual volume (low, medium, high), which represents the number of PNs performed at each participating institution during each study calendar year.

2.4 Statistical analyses

First, differences in medians and proportions were assessed by, respectively, the Kruskal-Wallis and the chi-square tests. Second, estimated annual percentage changes (EAPC) tested temporal trends of MetS and individual MetS components. Third, overall and specific complication rates were tested in separate multivariable logistic regression models. All multivariable models relied on generalized estimating equations to further adjust for clustering [26]. Subsequently, data distribution was adjusted according to the provided NIS population weights to render estimates more accurate nationally [26]. Multivariable models were fully adjusted for the concomitant presence of all four MetS components. Moreover, we expanded the extent of previous analyses, not only by combining all possible MetS components among risk factors, but also by testing for dose-response from the concomitant effect of multiple MetS components.

All statistical tests were two-sided with a level of significance set at $p<0.05$. All analyses were performed using the R software environment for statistical computing and graphics (version 3.4.1; http://www.r-project. org/).

3. Results

3.1 Descriptive analyses and trends over time

Of 25,875 patients: 1) 59.3% had high blood pressure, 2) 14.7% had BMI≥30, 3) 21.7% had altered fasting glucose, 4) 20.2% had high triglycerides and 5) <0.01% had low HDL cholesterol (Supplementary Figure 1). Respectively, one vs. two vs. three vs. four MetS components were recorded in 34.9% vs. 22.9% vs. 8.9% vs. 2.2% patients. Of all patients, 11.1% exhibited ≥3 components and qualified for MetS diagnosis (Table 1).

Time trends revealed an increase in the rates of patients with ≥3 MetS components (MetS definition; EAPC:+12.0%;p<0.001; Supplementary Figure 2a). Similarly, the rates of high blood pressure (EAPC:+1.4%;p<0.001; Supplementary Figure 2b), BMI≥30 (EAPC:+10.5%;p<0.001; Supplementary Figure 2c), altered fasting glucose (EAPC:+2.8%;p<0.002; Supplementary Figure 2d) and high triglycerides (EAPC:+10.7%;p<0.001; Supplementary Figure 2e) increased over time.

3.2 Crude rates of overall and specific complications according to type of MetS components

Patients with high blood pressure exhibited higher rates of overall complications (36.0 vs. 26.8%;p<0.001). Specifically, patients with high blood pressure exhibited higher rates of transfusions, as well as a higher rates of cardiac, miscellaneous medical, vascular, respiratory and gastrointestinal complications (Supplementary table 2).

Patients with BMI≥30 exhibited higher rates of overall complications (37.7 vs. 31.3%;p<0.001). Specifically, patients with BMI≥30 exhibited higher rates of transfusions, as well as higher rates of cardiac, miscellaneous medical and respiratory complications.

Patients with altered fasting glucose exhibited higher rates of overall complications (38.2 vs. 30.6%;p<0.001). Specifically, patients with altered fasting glucose exhibited higher rates of transfusions, as well as higher rates of cardiac, miscellaneous medical, respiratory and gastrointestinal complications.

Patients with high triglycerides exhibited higher rates of overall complications (38.2 vs. 30.8%; p<0.001). Specifically, patients with high triglycerides exhibited higher rates of transfusions, as well as higher rates of cardiac, miscellaneous medical, vascular, respiratory and gastrointestinal complications.

3.3 Multivariable analyses according to type of MetS components

In multivariable logistic regression models predicting overall complications (Table 2), high blood pressure (Odds ratio [OR]:1.19;p<0.001), BMI≥30 (OR:1.40;p<0.001), altered fasting glucose (OR:1.14;p<0.001) and high triglycerides (OR:1.14;p<0.001) achieved independent predictor status. Specifically, all four examined MetS components achieved independent predictor status in analyses addressing cardiac and miscellaneous medical complications, as well as transfusions. In analyses addressing vascular complications, respectively only BMI≥30 and high triglycerides achieved independent predictor status. In analyses addressing respiratory, infectious and wound complications only BMI≥30 achieved independent predictor status. Conversely, in analyses focusing on intraoperative, gastrointestinal, genitourinary and miscellaneous surgical complications, none of the four examined MetS components achieved independent predictor status. Subgroup analyses according to PN surgical approach, namely open vs. laparoscopic/robotic patients, are reported in Supplementary Table 4.

3.4 Crude rates of overall and specific complications according to number of MetS components

Overall complication rates were, respectively, 25.4% vs. 32.4% vs. 36.8% vs. 40.7% vs. 44.8% in patients with zero vs. one vs. two vs. three vs. four MetS components (Figure 1a). Specifically, significant increasing rates of cardiac (Figure 1b), miscellaneous medical (Figure 1d), vascular (Figure 1e), respiratory complications (Figure 1f), as well as transfusions (Figure 1b) were observed in patients with, respectively, zero vs. one vs. two vs. three vs. four MetS components. Conversely, no significant trends were observed between the number of MetS components and the

rates of intraoperative, gastrointestinal, genitourinary, infectious, wound and miscellaneous surgical complications (Supplementary table 3).

3.5 Multivariable analyses according to number of MetS components: dose-response effect

In multivariable logistic regression models, the ORs indicating the association between the number of MetS components and overall complication rates, demonstrated a gradual increase in the strength of the association when one (OR:1.23;p<0.001), two (OR:1.44;p<0.001), three (OR:1.77; p<0.001) or four (OR:2.13;p<0.001) MetS components were recorded in each individual patient, respectively (Table 3). In eleven analyses focusing on specific complications rates, five revealed presence of a dose-response effect. Specifically, a dose-response effect was observed in multivariable logistic regression models addressing cardiac, miscellaneous medical, vascular and respiratory complications, as well as transfusions. Conversely, in the six remaining models focusing on intraoperative, gastrointestinal, genitourinary, infectious, wound and miscellaneous surgical complications, no dose-response effect was identified.

Subgroup analyses according to PN surgical approach, namely open vs. laparoscopic/robotic patients, are reported in Supplementary Table 5.

4. Discussion

The association between MetS and early adverse perioperative outcomes after PN has been poorly investigated [5–9]. However, obesity [10,12–15,17], hypertension [20,21] and diabetes [21,23–25] have been previously related to higher complication rates after PN. These analyses did not account for the simultaneous effect of other MetS components. In consequence, they could not validate an independent predictor status for each component in isolation, when the effect of other MetS components is accounted for. Finally, these analyses could not test the possibility of a dose-response relationship when >1 MetS component is at play. Based on these limitations, we examined the relationship between four established MetS components (high blood pressure, BMI≥30, altered fasting glucose and high triglycerides) and perioperative complications after PN. We hypothesized that presence of one and, to an even greater extent of multiple MetS components, may predispose to higher complication rates after PN. Our results showed several important findings.

First, MetS patients account for, approximately, 11% of contemporary PN series. Moreover, the rates of MetS diagnosis based on presence of at least three MetS components (EAPC:+12.0%) and the rates of MetS single components increased over time. Our results corroborate previous National Health and Nutrition Examination Survey (NHANES) data [2] and validate the notion that the increasing rates of MetS is gaining in momentum.

Second, each of the four examined MetS components (high blood pressure, BMI≥30, altered fasting glucose and high triglycerides) achieved independent predictor status as unique risk variables in four out of twelve multivariable models predicting overall, cardiac and miscellaneous medical complications, as well as transfusions, even after full adjustment for patient and hospital characteristics, as well as after full adjustment for other MetS components. Moreover, BMI≥30 was also associated with higher rates of vascular, respiratory, infectious and wound complications. Additionally, high triglycerides were also associated with higher rates of vascular complications. Finally, no meaningful differences were observed in subgroup analyses according to open vs. laparoscopic/robotic PN approach. Our findings build upon previous reports, where individual MetS

components have been examined, but were never tested after full adjustment for the effect of the remaining MetS components [10,13–15,21,23–25]. To the best of our knowledge, we are the first to demonstrate the individual ability of each MetS component, even when all others components are fully accounted for. Our findings indicate that in the context of PN early perioperative outcomes, presence of one or several MetS components may identify individuals at higher risk of perioperative complications. Our database allowed us to examine the effect of each MetS component when it was coded in a dichotomized fashion (normal vs. abnormal). Unfortunately, we have no access to continuously coded values for the five MetS components. It is possible that additional predictive information may be derived from an analysis that relies on continuously coded MetS components.

Third, unlike in previous analyses, we tested for dose-response effect and confirmed that an increasing number of MetS components is directly proportional to the magnitude of six out of twelve examined endpoints: overall, cardiac, miscellaneous medical, vascular and respiratory complications, as well as transfusions. The magnitude of the dose-response effect was strongest in analyses addressing overall and cardiac complications, it was intermediate in analyses addressing transfusions and miscellaneous medical complications and it was weakest in analyses addressing vascular and respiratory complications. Despite the variable effect on the magnitude of adverse perioperative outcomes, all dose-response relationships demonstrated independent predictor status for each unit increase in the number of present MetS components. These observations are particularly important, since they illustrate that even the presence of one MetS component is associated with higher risk of perioperative complications. Therefore, patients who do not yet meet the diagnosis of MetS, based on presence of one or only two MetS components, should still be considered at an elevated risk of early adverse events after PN and represent candidates for preventative measures, if applicable. For example, pre-operative nutrition therapies, lifestyle changes and statins use could represent preventive measures that may modify peri-anaesthetic and surgical risks in MetS patients [29]. Last but not least, findings of this work failed to show statistically significant associations between surgical approach (namely: open vs. laparoscopic/robotic PN) and

perioperative complications among patients with MetS. In consequence, MetS patients should be properly informed about the risk of higher perioperative complications after PN, regardless of surgical approach proposed.

Fourth, it is important to emphasize differences in MetS rates according to its definition within retrospective analyses. In all such initiatives, MetS presence is established based on its five components, which may be identified using specific diagnostic codes. Even though we relied on a standardized definition [1,27,28] to identify each of the five MetS components, we recorded a very low rate of low HDL cholesterol levels. Different prevalence rates of low HDL cholesterol and of other MetS components have been reported by several investigators [2,7,9]. Moreover, MetS patients could be more frequently addressed to other nonsurgical option, that are usually reserved to surgical unfit patients. Therefore, MetS should ideally be examined within a prospectively gathered database designed with this intent. Until such analysis has been completed, it will be difficult to validly explain discrepancies observed in various retrospective databases. Nonetheless, the overwhelming agreement between all analyses about the importance of MetS components with respect to their associations with perioperative complications after PN, convincingly implicates either individual MetS components or their combined effect in the association with these adverse endpoints. Our findings are also supported by previous findings from other surgical areas. Specifically, MetS was associated with higher rates of perioperative complications in non-oncological patients treated with cardiovascular, neurosurgical or orthopedic surgery [28,29]. Moreover, higher rates of perioperative adverse events had been observed in surgically treated MetS patients with breast, colorectal or liver cancer[27,29].

Taken together, to the best of our knowledge, we provided the first large scale attempt to test the ability of MetS, defined according to the International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute [1], to predict worse overall and specific perioperative complications, in PN treated patients. Our analyses showed that MetS patients accounted for almost 11% of the PN population and that the proportion of MetS patients increased

over time. Moreover, MetS components achieved independent predictor status in multivariable models addressing overall and several specific perioperative complications, even after adjustment for patient and hospital characteristics, as well as adjustment for other MetS components. Last but not least, a dose-response effect was observed when MetS components were combined into five risk strata. In consequence, MetS may qualify as an important risk factor for identification of patients at risk for higher rates of perioperative complications after PN.

Despite its novelty, our study has limitations. First, the data are retrospective. In consequence, our analysis represents a weak substitute for prospective randomized comparisons between MetS vs. non-MetS patients treated with PN. Second, within the NIS database [26], complications are limited to in-hospital events. In consequence, delayed complications, as well as the readmission rate, could not be examined. Third, information on performance status, ASA score, lookback period of CCI assessment, as well as laboratory values, are not available within the NIS database. Finally, since the NIS database does not provide tumor characteristics, such as stage and grade, we were unable to adjust our analyses for these variables.

5. Conclusion

MetS and its components consistently and strongly predict perioperative complications after PN. Moreover, the strength of the effect was directly proportional to the number of MetS components exhibited by each individual patient, even if formal MetS diagnosis of ≥3 components has not been met.

6. References

1. Alberti KGMM, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: A joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American heart association; World heart federation; International . *Circulation*. 2009;120(16):1640-1645. doi:10.1161/CIRCULATIONAHA.109.192644

2. Aguilar M, Bhuket T, Torres S, Liu B, Wong RJ. Prevalence of the metabolic syndrome in the United States, 2003-2012. *Jama*. 2015;313(19):1973-1974. doi:10.1001/jama.2015.4260

3. Keehn A, Srivastava A, Maiman R, et al. The relationship between visceral obesity and the clinicopathologic features of patients with small renal masses. *J Endourol*. 2015;29(3):372-376. doi:10.1089/end.2014.0512

4. Kocher NJ, Rjepaj C, Robyak H, Lehman E, Raman JD. Hypertension is the primary component of metabolic syndrome associated with pathologic features of kidney cancer. *World J Urol*. 2017;35(1):67-72. doi:10.1007/s00345-016-1850-2

5. Selph JP, Whited WM, Smith AB, et al. Metabolic Syndrome as a Predictor for Postoperative Complications after Urologic Surgery. *Urology*. 2014;83(5):1051-1059. doi:10.1016/j.urology.2014.01.014

6. Hagiwara M, Miyajima A, Hasegawa M, et al. Visceral obesity is a strong predictor of perioperative outcome in patients undergoing laparoscopic radical nephrectomy. *BJU Int*. 2012;110(11 C). doi:10.1111/j.1464-410X.2012.11274.x

7. Martín OD, Bravo H, Arias M, Dallos D, Quiroz Y. Determinant factors for chronic kidney disease after partial nephrectomy. *Oncoscience*. 2018;5(January). doi:10.18632/oncoscience.393

8. Ioffe E, Hakimi AA, Oh SK, et al. Effect of visceral obesity on minimally invasive partial nephrectomy. *Urology*. 2013;82(3):612-619. doi:10.1016/j.urology.2013.04.058

9. Hua X, Ying-Ying C, Zu-Jun F, et al. Obesity, hypertension and diabetes mellitus affect complication rate of different nephrectomy techniques. *Actas Urológicas Españolas (English Ed*. 2014;38(10):640-646. doi:10.1016/j.acuroe.2014.10.003

10. Anast JW, Stoller ML, Meng M V., et al. Differences in complications and outcomes for obese patients undergoing laparoscopic radical, partial or simple nephrectomy. *J Urol*. 2004;172(6 I):2287-2291. doi:10.1097/01.ju.0000143820.56649.a4

11. Gong EM, Orvieto MA, Lyon MB, Lucioni A, Gerber GS, Shalhav AL. Analysis of Impact of Body Mass Index on Outcomes of Laparoscopic Renal Surgery. *Urology*. 2007;69(1):38-43. doi:10.1016/j.urology.2006.09.020

12. Bensalah K, Raman JD, Bagrodia A, Marvin A, Lotan Y. Does Obesity Impact the Costs of Partial and Radical Nephrectomy? *J Urol*. 2008;179(5):1714-1718. doi:10.1016/j.juro.2008.01.035

13. Eaton SH, Thirumavalaven N, Katz MH, Babayan RK, Wang DS. Effect of body mass index on perioperative outcomes for laparoscopic partial nephrectomy. *J Endourol*. 2011;25(9):1447-1450. doi:10.1089/end.2010.0664

14. Isac WE, Autorino R, Hillyer SP, Hernandez A V., Stein RJ, Kaouk JH. The impact of body mass index on surgical outcomes of robotic partial nephrectomy. *BJU Int*. 2012;110(11 C):1-6. doi:10.1111/j.1464-410X.2012.11318.x

15. Kiziloz H, Dorin R, Finnegan KT, Shichman S, Meraney A. The impact of body mass index on perioperative outcomes in robot-assisted laparoscopic partial nephrectomy. *J Endourol*. 2013;27(8):1000-1007. doi:10.1089/end.2012.0665

16. Richards KA, Negron E, Cohn JA, Steinberg Z, Eggener SE, Shalhav AL. The impact of body mass index on renal functional outcomes following minimally invasive partial nephrectomy. *J Endourol*. 2014;28(11):1338-1344. doi:10.1089/end.2014.0360

17. George AK, Rothwax JT, Herati AS, et al. Perioperative Outcomes of Laparoscopic Partial Nephrectomy Stratified by Body Mass Index. *J Endourol*. 2015;29(9):1011-1017. doi:10.1089/end.2014.0725

18. Sperling CD, Xia L, Berger IB, Shin MH, Strother MC, Guzzo TJ. Obesity and 30-Day Outcomes Following Minimally Invasive Nephrectomy. *Urology*. 2018;121:104-111. doi:10.1016/j.urology.2018.08.002

19. Satasivam P, Reeves F, Rao K, et al. Patients with medical risk factors for chronic kidney disease are at increased risk of renal impairment despite the use of nephron-sparing surgery. *BJU Int*. 2015;116(4):590-595. doi:10.1111/bju.13075

20. Isharwal S, Ye W, Wang A, et al. Impact of Comorbidities on Functional Recovery from Partial Nephrectomy. *J Urol*. 2018;199(6):1433-1439. doi:10.1016/j.juro.2017.12.004

21. Beksac AT, Reddy BN, Martini A, et al. Hypertension and diabetes mellitus are not associated with worse renal functional outcome after partial nephrectomy in patients with normal baseline kidney function. *Int J Urol*. 2019;26(1):120-125. doi:10.1111/iju.13819

22. Bhindi B, Lohse CM, Schulte PJ, et al. Predicting Renal Function Outcomes After Partial and Radical Nephrectomy(Figure presented.). *Eur Urol*. 2019;75(5):766-772. doi:10.1016/j.eururo.2018.11.021

23. Yang H, Yin K, Wang Y, et al. Pre-existing type 2 diabetes is an adverse prognostic factor in patients with renal cell carcinoma. *J Diabetes*. 2019;(May):1-9. doi:10.1111/1753-0407.12957

24. Richstone L, Montag S, Ost MC, et al. Predictors of hemorrhage after laparoscopic partial nephrectomy. *Urology*. 2011;77(1):88-91. doi:10.1016/j.urology.2008.05.022

25. Höfner T, Zeier M, Hatiboglu G, et al. The impact of type 2 diabetes on the outcome of localized renal cell carcinoma. *World J Urol*. 2014;32(6):1537-1542. doi:10.1007/s00345-013-1231-z

26. Healthcare Cost and Utilization Project (HCUP). HCUP NIS Database Documentation. Agency for Healthcare Research and Quality, Rockville, MD.

27. Akinyemiju T, Sakhuja S, Vin-Raviv N. In-Hospital Mortality and Post-Surgical Complications Among Cancer Patients with Metabolic Syndrome. *Obes Surg*. 2018;28(3):683-692. doi:10.1007/s11695-017-2900-6

28. Memtsoudis SG, Kirksey M, Ma Y, et al. Metabolic syndrome and lumbar spine fusion surgery: Epidemiology and perioperative outcomes. *Spine (Phila Pa 1976)*. 2012. doi:10.1097/BRS.0b013e31823a3a13

29. Tzimas P, Petrou A, Laou E, Milionis H, Mikhailidis DP, Papadopoulos G. Impact of metabolic syndrome in surgical patients: Should we bother? *Br J Anaesth*. 2015;115(2):194-202. doi:10.1093/bja/aev199

Figure legends

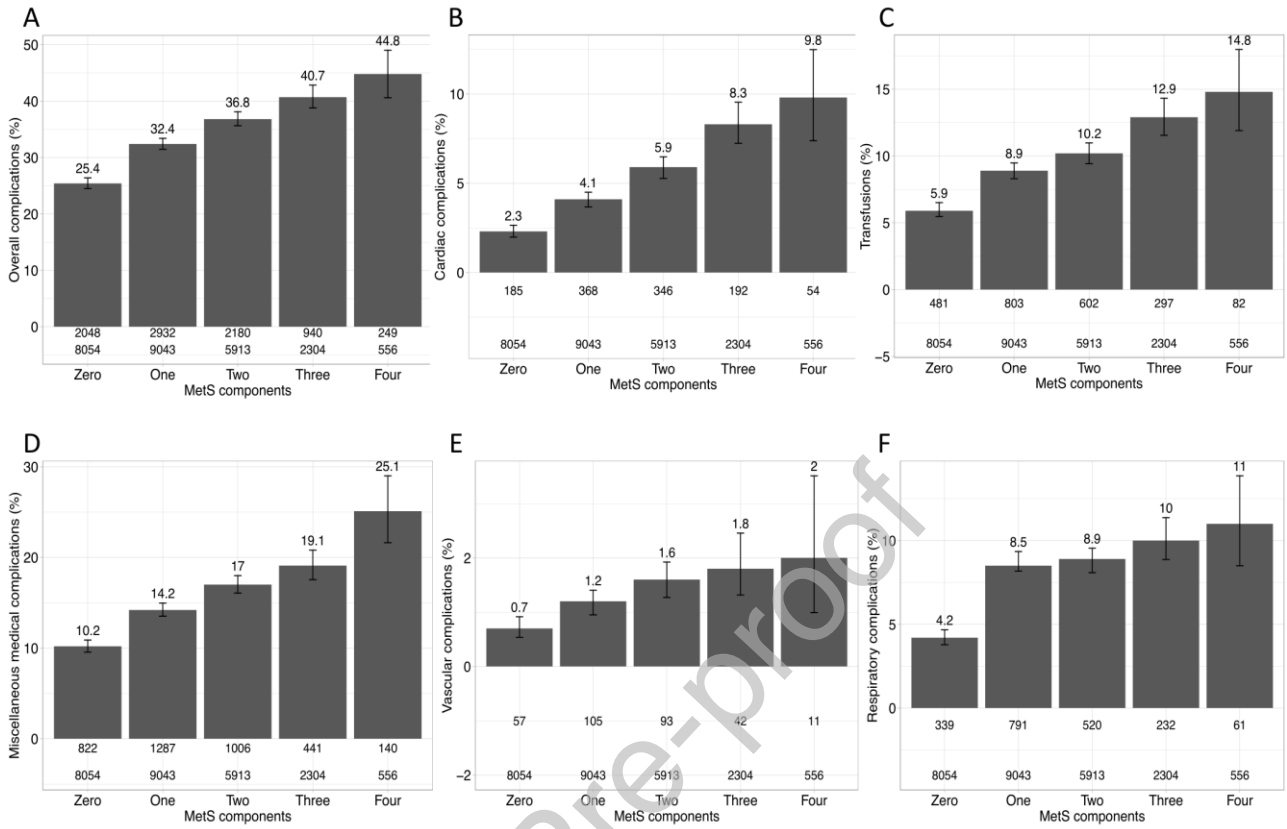

Figure 1. Barplots depicting crude rates of overall and specific complications, according to number of metabolic syndrome components, in 25,875 partial nephrectomy patients (unweighted population) identified within National (Nationwide) Inpatient Sample (NIS) database from 2000 to 2015.

A) Overall complications; B) Cardiac complications; C) Transfusions; D) Miscellaneous medical complications; E) Vascular complications; F) Respiratory complications

Table 1. Descriptive characteristics of 25,875 partial nephrectomy patients (unweighted population) identified within National (Nationwide) Inpatient Sample (NIS) database from 2000 to 2015 and stratified according to presence or absence of metabolic syndrome. IQR: interquartile range; CCI: Charlson Comorbidity Index

		Metabolic syndrome: Yes (n=2,878; 11.1%)	**Metabolic syndrome: No** (n=22,997; 88.9%)	**p-value**
Age (years)	Median (IQR)	63 (56-70)	60 (50-68)	**<0.001**
Gender, n (%)	Male	1,701 (59.1)	14,299 (62.2)	**0.001**
	Female	1,177 (40.9)	8,698 (37.8)	
Ethnicity, n (%)	Caucasian	1,878 (65.3)	15,069 (65.5)	**<0.001**
	African-American	322 (11.2)	2,016 (8.8)	
	Other	678 (23.6)	5,912 (25.7)	
CCI, n (%)	0-1	1,975 (68.6)	20,977 (91.2)	**<0.001**
	≥2	903 (31.4)	2,020 (8.8)	
Surgical approach, n (%)	Open	1,848 (64.2)	16,005 (69.6)	**<0.001**

	Laparoscopic	138 (4.8)	1,457 (6.3)	
	Robotic	892 (31)	5,535 (24.1)	
Year of diagnosis, n (%)	2000-2007	400 (13.9)	7,756 (33.7)	**<0.001**
	2008-2015	2,478 (86.1)	15,241 (66.3)	
Lymphadenectomy, n (%)	No	2,860 (99.4)	22,812 (99.2)	0.4
	Yes	18 (0.6)	185 (0.8)	
Insurance status, n (%)	Medicare	1,306 (45.4)	8,152 (35.4)	**<0.001**
	Medicaid	173 (6)	1,346 (5.9)	
	Private	1,271 (44.2)	12,218 (53.1)	
	Other	128 (4.4)	1,281 (5.6)	
Region, n (%)	Midwest	802 (27.9)	5,020 (21.8)	**<0.001**
	Northeast	576 (20)	5,824 (25.3)	
	South	1,018 (35.4)	8514 (37)	
	West	482 (16.7)	3,639 (15.8)	

Income, n (%)	1st quantile	728 (25.3)	5,208 (22.6)	**<0.001**
	2nd quantile	726 (25.2)	5,197 (22.6)	
	3rd quantile	750 (26.1)	5,779 (25.1)	
	4th quantile	674 (23.4)	6,813 (29.6)	
Annual hospital volume, n (%)	Low	810 (28.1)	7,800 (33.9)	**<0.001**
	Medium	966 (33.6)	7,198 (31.3)	
	High	1,102 (38.3)	7,999 (34.8)	
Teaching status, n (%)	Teaching	2,111 (73.3)	16,872 (73.4)	0.9
	Non teaching	767 (26.7)	6,125 (26.6)	
Hospital bedsize, n (%)	Small	307 (10.7)	2,360 (10.3)	0.4
	Medium	575 (20)	4,422 (19.2)	
	Large	1,996 (69.4)	16,215 (70.5)	

Table 2. Separate multivariable logistic regression models predicting overall and specific complications in patients treated with partial nephrectomy for renal cell carcinoma within the National Inpatient Sample database (2000-2015), according to presence or absence of metabolic syndrome components. All models were weighted and adjusted for clustering, as well as age, year of surgery, gender, ethnicity, insurance status, teaching status, hospital volume, region, hospital bed-size, income, lymph node dissection, surgical approach, as well as for all four examined metabolic syndrome components. OR=odds ratio, CI=confidence interval

	High blood pressure (Yes vs. No)		**BMI≥30 (Yes vs. No)**		**Altered fasting glucose (Yes vs. No)**		**High triglycerides (Yes vs. No)**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
OVERALL	1.19 (1.12-1.27)	**<0.001**	1.40 (1.29-1.51)	**<0.001**	1.14 (1.07-1.21)	**<0.001**	1.14 (1.06-1.22)	**<0.001**
CARDIAC	1.14 (1.00-1.33)	**0.03**	1.68 (1.43-1.98)	**<0.001**	1.73 (1.51-1.97)	**<0.001**	1.20 (1.04-1.38)	**0.01**
TRANSFUSIONS	1.22 (1.10-1.36)	**<0.001**	1.34 (1.10-1.40)	**<0.001**	1.35 (1.22-1.50)	**<0.001**	1.11 (1.02-1.23)	**0.03**
MISCELLANEOUS MEDICAL	1.24 (1.14-1.35)	**<0.001**	1.23 (1.11-1.35)	**<0.001**	1.18 (1.09-1.29)	**<0.001**	1.13 (1.03-1.23)	**0.005**
VASCULAR	1.13 (0.85-1.49)	0.3	1.45 (1.05-1.99)	**0.02**	0.83 (0.63-1.10)	0.2	1.74 (1.33-2.28)	**<0.001**
RESPIRATORY	1.07 (0.96-1.19)	0.1	1.34 (1.18-1.52)	**<0.001**	1.01 (0.91-1.13)	0.7	1.06 (0.95-1.19)	0.2
INTRAOPERATIVE	1.12 (0.92-1.36)	0.2	1.13 (0.87-1.46)	0.3	0.85 (0.68-1.07)	0.1	0.79 (0.61-1.02)	0.07
GASTROINTESTINAL	0.97 (0.87-1.07)	0.5	0.96 (0.84-1.09)	0.5	1.03 (0.92-1.15)	0.5	1.08 (0.97-1.21)	0.1
GENITOURINARY	0.95 (0.80-1.12)	0.5	1.15 (0.92-1.43)	0.2	0.96 (0.79-1.15)	0.6	0.91 (0.76-1.11)	0.3
INFECTIOUS	0.65 (0.49-1.01)	0.7	1.66 (1.17-2.36)	**0.004**	0.96 (0.72-1.29)	0.8	0.91 (0.63-1.41)	0.9
WOUND	0.93 (0.66-1.19)	0.4	1.58 (1.04-2.42)	**0.03**	0.70 (0.47-1.04)	0.08	1.67 (0.42-1.05)	0.08

MISCELLANEOUS SURGICAL	0.96 (0.83-1.10)	0.5	1.13 (0.94-1.35)	0.1	0.85 (0.73-1.01)	0.06	0.94 (0.80-1.10)	0.4

Table 3. Separate multivariable logistic regression models predicting overall and specific complications in patients treated with partial nephrectomy for renal cell carcinoma within the National Inpatient Sample database (2000-2015), according to number of metabolic syndrome components. All models were weighted and adjusted for clustering, as well as age, year of surgery, gender, ethnicity, insurance status, teaching status, hospital volume, region, hospital bed-size, income, lymph node dissection, surgical approach. OR=odds ratio, CI=confidence interval

	One vs. Zero components		**Two vs. Zero components**		**Three vs. Zero components**		**Four vs. Zero components**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
OVERALL	1.23 (1.15-1.32)	**<0.001**	1.44 (1.34-1.56)	**<0.001**	1.77 (1.60-1.97)	**<0.001**	2.13 (1.78-2.54)	**<0.001**
CARDIAC	1.27 (1.05-1.53)	**0.01**	1.80 (1.48-2.19)	**<0.001**	2.86 (2.27-3.59)	**<0.001**	3.73 (2.68-5.19)	**<0.001**
TRANSFUSIONS	1.27 (1.12-1.43)	**<0.001**	1.41 (1.23-1.61)	**<0.001**	1.92 (1.63-2.26)	**<0.001**	2.34 (1.80-3.05)	**<0.001**
MISCELLANEOUS MEDICAL	1.23 (1.11-1.35)	**<0.001**	1.42 (1.28-1.57)	**<0.001**	1.64 (1.44-1.88)	**<0.001**	2.42 (1.97-2.98)	**<0.001**
VASCULAR	1.22 (1.00-1.72)	**0.04**	1.55 (1.07-2.24)	**0.01**	1.90 (1.24-2.91)	**0.003**	2.13 (1.11-4.06)	**0.02**
RESPIRATORY	1.18 (1.04-1.35)	**0.001**	1.18 (1.03-1.36)	**0.01**	1.41 (1.19-1.67)	**<0.001**	1.56 (1.16-2.10)	**0.003**
INTRAOPERATIVE	1.10 (0.89-1.37)	0.3	1.05 (0.82-1.35)	0.6	0.96 (0.66-1.39)	0.8	0.53 (0.23-1.25)	0.1

GASTROINTESTINAL	1.05 (0.93-1.17)	0.3	1.00 (0.87-1.14)	0.9	1.03 (0.87-1.22)	0.7	1.20 (0.90-1.59)	0.1
GENITOURINARY	0.93 (0.77-1.12)	0.4	0.88 (0.71-1.08)	0.2	0.78 (0.57-1.06)	0.1	0.89 (0.52-1.53)	0.6
INFECTIOUS	0.71 (0.57-1.07)	0.1	0.66 (0.42-1.11)	0.2	0.92 (0.76-1.18)	0.4	1.02 (0.46-2.25)	0.9
WOUND	0.69 (0.48-1.00)	0.05	0.64 (0.35-1.16)	0.2	0.62 (0.34-1.14)	0.1	0.79 (0.27-2.27)	0.6
MISCELLANEOUS SURGICAL	0.95 (0.81-1.11)	0.5	0.93 (0.78-1.11)	0.4	0.91 (0.72-1.17)	0.4	0.69 (0.42-1.14)	0.1