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Endoscopic Submucosal Dissection for Gastric Superficial Lesions

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Endoscopic Submucosal Dissection for Gastric Superficial Lesions

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Área: Gastrenterologia

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Professor Doutor Pedro Pimentel Nunes

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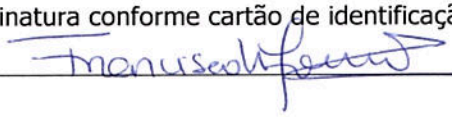

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ABSTRACT

Background and aims: Endoscopic Submucosal Dissection (ESD), an endoscopic technique used for treatment of gastric superficial lesions, has been gaining importance on western countries. Procedural times have an impact on various outcomes. Our aim is to define which factors from patients, lesions and procedure can predict longer procedural times.

Methods: In a cohort of 127 lesions resected by ESD with IT-knife by experienced gastroenterologists, characteristics from the patient (age, gender, presence of co-morbidities, usage and suspension of anti-platelet drugs and general physical condition), lesion (size, histopathological diagnosis at biopsy, location, macroscopic type and submucosal invasion) and procedure (complications) were retrospectively analyzed for its impact on time of procedure. Univariate and multivariate analysis were performed.

Results: Lesions larger than 20mm ($p<0.001$), on the upper third of the stomach ($p=0.035$) and with an ASA score of 3 ($p=0.031$) were considered influential factors for a longer procedure time and specifically for a time of procedure longer than 90 minutes. Existence of intra-procedure complications was also a predictor for a procedure time >90 minutes. Lesion's size >20mm and location in the upper third were independently associated with a procedure time longer than 90 minutes (OR 4.91[95%CI 2.29-10.50] and OR 18.26 [95%CI 2.02-164.78], respectively)

Conclusion: The time of procedure of ESD for gastric superficial lesions is influenced by size of lesion (>20 mm) and location (upper third of stomach), which predict a time longer than 90 minutes. This can be useful for better management of workflow, operation, training of teams and anesthesic procedures.

KEYWORDS: stomach neoplasms, gastric cancer, endoscopic gastrointestinal surgical procedures, length of operative time

INTRODUCTION

Endoscopic Submucosal Dissection (ESD) is an endoscopic technique used for treatment of gastric superficial lesions [1]. It has been widely used in countries such as Korea and Japan, but its use only widespread in the Western countries in the last decade [2]. Although having successful results [3-5], ESD requires a high level of expertise in order to reach the desired outcomes [6, 7] .

Specifically, longer procedural times are related to a higher level of complications [8] such as delayed bleeding [9], perforation [10, 11], post-operative pneumonia [11-13] and other clinical complications related to premedication and a heavy workload for patients [7]. Moreover, previous retrospective studies have shown that time of procedure can be influenced by different factors such as existence of fibrosis [14, 15], presence of ulceration [7, 15-17], area of the resected specimen [7, 16-19], location on the upper portion of the stomach [7, 16-19], adhesion [19] and presence of a scar [7]. Therefore, it is essential to take these factors into account in the pre-operatory period, since they can influence the workflow for ESD such as allocation of type of rooms and anesthesic procedures, and level of training of teams [11].

The present work aims at addressing the procedure time of ESD for removal of superficial gastric lesions and to define which patients' characteristics, lesions' features and procedure variables may be predictive of longer procedural times.

MATERIALS AND METHODS

A. Type of study and selection of patients

Our study reports a retrospective cohort of 162 consecutively patients (with 195 gastric neoplastic lesions) that were referred to the Portuguese Institute of Oncology – Porto (IPO) from March 2003 to April 2013 for assessment and treatment of gastric superficial neoplasias. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, in compliance with good clinical practice.

All patients were referred for endoscopic treatment after a multidisciplinary oncology group decision and full medical and anesthesiology evaluation. Both oral and written informed consent was given by patients. All the endoscopic procedures performed on IPO during this period were screened by their report on the institute database, followed by analysis of the clinical record of the patient.

For the purpose of this study, only cases treated by ESD, without ulcerative findings on the lesion, and technically performed with IT-knife were selected. Fifty three procedures were excluded because they were treated by Endoscopic Mucosal Resection (EMRc). Of the ESD procedures, one was excluded because Flex-knife was used along with IT knife, six were excluded because Diathermic loop was used along with IT-knife and two were excluded because cap was used along with IT-Knife. Six procedures were excluded due to incomplete information regarding time of procedure.

B. Description of endoscopic resection techniques

Two operators effectuated the endoscopic procedures (MDR and PPN). MDR received training in Japan and in live animal courses before introducing the technique in the Hospital. PPN had animal training and then gradually begun the endoscopic procedures under MDR supervision in 2010 [20, 21]. Lateral margins of each lesion were always determined by chromoendoscopy with indigo carmine 1% [22-24] or with virtual chromoendoscopy using HR-NBI (applying Pimentel-Nunes *et al* classification for delimitation of lesions [25]) and small marks were made 2-5 mm from the edges of the lesion using needle-knife coagulation. The technique of Endoscopic Submucosal Dissection (ESD) was initiated after the submucosal injection of the lesion with an epinephrine and saline solution (1:100000) and a few drops of methylene blue. After that to obtain access to the submucosal layer 3 to 4 small mucosal incisions using needle-knife were made. Then, an IT-knife (Olympus) in the Endocut mode was used to do the circumference of the lesion outside the coagulation markers. Complete dissection of the lesion was performed using Endocut mode (Olympus electrosurgical unit) with further submucosal injections as needed being made throughout the procedure.

All procedures were performed under deep sedation or general anesthesia (with propofol and fentanyl) supervised by an anesthesiology team.

C. Definitions: procedural time and potential predictive factors

Procedural time was defined as the time of anesthesia, in minutes, reported in patients' clinical files by the anesteshiology team. Thereafter, two groups were created according to a time shorter or longer than 90 minutes of procedure.

In order to determine the influential factors on procedure time the following variables were analyzed:

- **Regarding the lesion:** Gross cross-sectional dimension (measured endoscopically) in millimeters(mm), followed by sub-grouping in lesions ≤20 mm (absolute indication for endoscopic resection on differentiated lesions without ulcerative findings [26]) and >20 mm, histopathological findings at diagnostic biopsy (low-grade dysplasia, high grade dysplasia or

T1a), Location (upper, middle and lower third of the stomach), macroscopic type (organized by Paris classification [27], followed by sub-grouping in depressed and non-depressed lesions) and Histopathological definitive classification defined by the presence or absence of submucosal invasion.

- **Regarding the patient**: age, gender, presence of co-morbidities, previous suspension of anti-platelet drugs and general condition of the patient, evaluated by the American Society of Anaesthesiology score (ASA 1,2,3,4 or 5) [28].

- **Regarding the procedure:** existence and type of complications.

D. Statistical Analysis

Statistical Package for Social Sciences (SPSS 21.0 Package Facility, SPSS Inc, IL, USA) was used for data support and analysis. Analysis was performed using descriptive statistics methods, as well as Kruksal-Wallis test for analysis with time as a continuous variable, and Chi-Square and Fisher's Exact test for analysis of dichotomic variables. Logistic regression was used to estimate OR for individual variables in multivariate analysis. A value of $p<0.05$ was considered to be statistically significant.

RESULTS

Characteristics of lesions

Of the 127 lesions, 55% were performed on male patients with an average age of 69 (±10.9) years old and a median of 71 (IQR 61-77). Eight (6%) lesions were located on the upper third, 27 (21%) on the middle third and 92 (72%) were located on the lower third. The median time of procedure was of 85 minutes (IQR 55-130). The median tumor size was of 20 mm (IQR 15-30).

Factors predictive of ESD procedure time

Tumor size, location and the ASA score were significantly associated with procedure time (see Table 1). Specifically, a procedure for a lesion >20 mm, located at the upper third of the stomach and in a patient with an ASA of 3 were associated with longer procedure time, with results significantly different from the other characteristics on the same group. Other patients', lesions' and characteristics of procedure are shown on Table 1.

Procedures were furthermore analysed in two different groups - those taking less than and those taking more than 90 minutes. These results are consistent with the findings on the previous analysis, as the majority of the cases (72%) with a lesion ≤20 mm lasted 90 minutes or less, while the majority of the cases with a lesion >20 mm (66%) lasted for more than 90 minutes (p<0,001). Also, lesions located on the upper third took more than 90 minutes (88%), compared to lesions at other locations (p<0.035) and gross majority of lesions in patients with ASA1 took less than 90 minutes to remove (74%) while lesions on patients with ASA 3 took more than 90 minutes on 60% of the cases (p=0,031). Moreover, this analysis also shows that intra-procedure complications pushed the procedure time to more than 90 minutes as 71% of the procedures with complications took more than 90 minutes (p=0.018). In multivariate analysis (Table 2), those patients harbouring lesions larger than 20 mm and located to the upper third showed an increased risk of 4.91 times [95% CI 2.29-10.50] and 18.26 times [95% CI 2.02-164.78], respectively and independently. The occurrence of complications during the

procedure and the ASA score do not seem to be independently predicting procedural time longer than 90 minutes.

DISCUSSION

To our knowledge this is the first study relating ESD time of procedure with factors from the lesion, patient and the procedure itself in Western countries. We showed that lesions with more than 20 mm, located on the upper third of the stomach and in patients with other co-morbidities have a time of procedure significantly higher than smaller lesions, on middle and lower stomach and in patients with less co-morbidities. Larger lesions and lesions on the upper third are independent predictors for longer procedure time. Our results may permit to establish these factors relevant for planning and management of these patients.

Predictive factors of prolonged time of procedure

Comparing the different characteristics of the lesions, a cross sectional dimension >20 mm had longer procedure times when compared to lesions ≤20 mm [120 (IQR 80-147.50) minutes *vs* 65 (IQR 45-110) minutes, p<0.001). Moreover, when the lesion was located on the upper third the median time was of 145 (IQR 115-253.75) minutes, significantly different from times recorded for lesions on the lower third with a median time of 80 (IQR 46.25-120) minutes, p=0.022. In what relates to the general condition of the patient, measured by the ASA Score, ASA 3 patients had a median procedure time of 120 (IQR 62.5-165) minutes, clearly longer than patients with ASA 1 with a median time of 65 (IQR 40-95) minutes, p=0.011. We also showed that these same characteristics tend to be associated with a procedure longer than 90 minutes. In fact, the size and location were independently associated with a time longer than 90 minutes whereas the risk profile of patients and/or the evidence of complications (bleeding) during the procedures were not independent.

The reasons why the first two factors can act as predictors for a longer time of procedure can be easily explained - a larger lesion will obviously require a higher area to be dissected and therefore more time; the location at the upper third, due to the position required for the scope and the wall characteristics, require more technical skills [7, 29, 30]. Nevertheless, for the other two factors we may

have different reasons not to observe them as independent predictive factors – bleeding is expected more often in lesions in the upper third [31] and ASA 3 patients prevalence is very low and they tend to be older [median age of 75 (IQR 69.5-80) *vs* 70 (IQR 59-76) on ASA 1 and 2, p=0.005] what may lead to larger [median dimension of 30 mm (IQR 18-30) on ASA 3 *vs* 20 mm (IQR 15-25) on ASA 1 and 2 , p=0.037] and more advanced lesions.

Predictive factors compared to western series

Moreover, the majority of our findings are in accordance with previous findings in eastern series, specifically in what regards to size and location of lesion [7, 15-19].

Goto et al. [16] have even developed a formula to predict the time of procedure based on size of lesion, location on the upper third and presence of ulceration. Comparing to our results, and considering the non-existence of ulcerated lesions on this series, for a lesion of 20 mm or more and located on the upper third, its predicted time of procedure is never less than 86 minutes which is in accordance with our findings that those two factors are associated with a procedure time longer than 90 minutes.

Ahn et al. [18] also presented results that are consistent with our findings as the predicted times of procedure for lesions on the upper third with more than 30 mm are always superior to 90 minutes. However, it doesn't have the same conclusion to lesions between 21 and 30 mm.

Regarding the intra-procedure complications predicting a longer time of procedure (>90 minutes) it is in agreement with previous findings by Yamamoto et al. [32] stating that uncontrolled hemorrhage makes the procedure lengthier.

We have also linked a higher ASA score to a prolonged procedure time. However, this finding contradicts Kim et al. [33] if we assume that a ASA 3 is similar to their's high risk group defined as having one or more co-morbidity states. However, it is not clear if this contradiction is real or if it is due to different classification systems and it was not confirmed as an independent factor.

Limitations

One of the limitations of our study has to do with the standard used to calculate time of procedure, based on the time of anesthesia. This means that our times of procedure can be slightly superior to the ones found on other studies that, for instance, count the time only on the beginning of lesion's marking. Nevertheless, the mean time of procedure on this series is similar to times reported on different eastern series. However, it can have an impact on the finding of the relation with the ASA score, as this one could relate directly to time of anesthesia and not with time of procedure. Also, it has also been reported on literature that many times the ASA Score is subjective to inter-observer variations [34]. Therefore, this finding should be looked with special attention.

However, future studies should focus on the analysis of time of anesthesia and time of procedure itself alone, evaluated at the same time, to give us a perspective on the impact of complications of the procedure itself or anesthesic complications on the global time.

Another limitation has to do with the evaluation of size being done with a cut-off point in the 20 mm, a methodological option that has to do with the size of our series not allowing comparisons in smaller groups.

A different limitation has to do with the fact that we only considered IT-knife for analysis for the scope of this study as previous studies refer that different knives have different times of procedure associated [35]. However, the option here was purely methodological as we had cases on our series with other knives, but the choice of other knives or concomitant knives with IT-knife was based on the fact that lesions were identified as more complicated and lengthy, that made us to opt to focus on only one knife, so this bias was not present on this study. Anyway, further studies comparing times of procedure with different knives can be an interesting are for research.

Finally, we do not have consistently recorded data for fibrosis and existence of scar throughout the observation period, bringing to the surface the limitation of this study being a retrospective study and subsequently the comparisons with other works. The definition of long-term prospective studies on this area with the focus on studying factors influencing time of procedure are the key for obtaining consistent and comparable data worldwide.

Conclusion

In summary, we found that lesions on the upper stomach, greater than 20 mm and in patients with significant co-morbidities can increase the time of procedure and it is expected that it will last more than 90 minutes, with the first two being independent predictors. It is important to keep in mind if these 3 factors are present on a certain lesion before the procedure, so an adequate planning of operation, human resources and anesthesic method can be performed, therefore allowing a increased efficacy and efficiency.

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		Time				
Characteristics	n	median (IQR)	p value	< 90 min	> 90 min	P value
Procedures (total)	127	85 (55-130)				
Gender			0.443			
Male	70	97.5 (50-140)		34(49%)	36(51%)	0.065
Female	57	80 (60-120)		37(65%)	20(35%)	
Age§	71 (61-77)		0.705			
<= 65	42	85 (43.75 -121.25)		25(60%)	17(40%)	0.564
>65	85	90 (60-140)		46 (54%)	39(46%)	
ASA			**0.011***			
ASA 1	31	65 (40-95)		23(74%)	8 (26%)	**0.031***
ASA 2	71	90 (55-130)		38(54%)	33 (46%)	
ASA 3	25	120 (62.50-165)		10(40%)	15(60%)	
Co-morbidities			0.125			
Yes	92	90 (30-112.75)		47(51%)	45(49%)	0.076
No	35	72.5 (55-140)		24(69%)	11(31%)	
Anti-platelets			0.153			
Yes	25	105 (60-187.5)		12(48%)	13(52%)	0.374
No	102	85 (48.75-126.25)		59(58%)	43(42%)	
Suspension of anti-platelets			0.764			

Yes	14	117.5 (60-200)	5(36%)	9(64%)	0.416
No	8	102.5 (52.50-201.25)	4(50%)	4(50%)	
Size of lesion		**<0.001**			
<= 20 mm	74	65 (45-110)	53(72%)	21(28%)	**<0.001**
>20 mm	53	120 (80-147.5)	18(34%)	35(66%)	
Histopathology at biopsy		0.521			
LGD	40	75 (46.25-125)	26(65%)	14(35%)	0.367
HGD	57	90 (52.50-137.50)	29(51%)	28(49%)	
Adenocarcinoma	30	90 (60-130)	16(53%)	14(47%)	
Type of lesion		0.891			
Naive	121	85 (55-130)	68(56%)	53(44%)	0.542
Recidive	6	95 (29.75-156)	3(50%)	3(50%)	
Location		**0.022****			
Upper third	8	145 (115-253.75)	1 (12%)	7(88%)	**0.035****
Middle third	27	90 (60-180)	15(56%)	12(44%)	
Lower third	92	80 (46.25-120)	55(60%)	37(40%)	
Macroscopic features		0.833			
Depressed lesions	60	87.5 (60-130)	36(60%)	24(40%)	0.379
Non depressed lesions	67	85 (45-140)	35(52%)	32(48%)	
Submucosal invasion		0.289			

Yes	14	115 (72.5-135)	6(43%)	8(57%)	0.297
No	113	85 (52.50-130)	65(58%)	48(42%)	
Complications		0.069			
Yes	17	130 (50-200)	5(29%)	12(71%)	**0.018**
No	110	84 (53.75-122.75)	66(60%)	44(40%)	

* Statistically significant for comparison between ASA1 and ASA3

** Statistically significant for comparison between Upper third and Lower third

§ Median Age (IQR)

IQR, interquartile range; min, minutes; LGD, Low-grade dysplasia; HGD, High-Grade dysplasia

TABLE 1 – Characteristics of patients, lesions and procedure with univariate analysis for predictors of longer procedure time and procedure time greater than 90 minutes.

		OR	(95%CI)	
Size	≤20 mm	1		
	> 20mm	**4.91**	**(2.29-10.50)**	**>0.001**
Location	Lower third	1		
	Middle third	1.182	(0.46-3.07)	0.731
	Upper third	**18.26**	**(2.02-164.78)**	**0.01**
Complications	No	1		
	Yes	2.84	(0.84-9.63)	0.093
ASA	1-2	1		
	3	1.713	(0.63-4.65)	0.292

OR, Odds Ratio; CI, Confidence Interval

TABLE 2 – Multivariate analysis of predictors for longer procedure time (>90 min)

ANEXOS

AGRADECIMENTOS

Ao Professor Doutor Mário Dinis Ribeiro por ter, desde cedo, alimentado o gosto pela investigação científica e por ter sido, mais do que o orientador deste trabalho, um orientador de todo o meu percurso académico e uma fonte de inspiração e encorajamento, nunca tendo desistido de acreditar na minha capacidade de trabalho.

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Acknowledgements

Acknowledgements should be made only to those who have made a substantial contribution to the study. Authors are responsible for obtaining written permission from people acknowledged by name in case readers infer their endorsement of data and conclusions.

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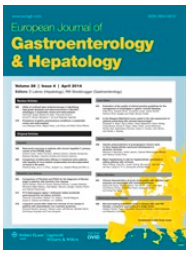

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c. Introduction

Provide a context or background for the study (that is, the

nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

d. Methods

The guiding principle of the Methods section should be clarity about how and why a study was done in a particular way. The section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section.

i. Selection and Description of Participants

Clearly describe the selection of observational or experimental participants (healthy individuals or patients, in¬cluding controls), including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age, sex, or ethnicity is not always known at the time of study design, researchers should aim for inclusion of representative populations into all study types and at a minimum provide descriptive data for these and other relevant demographic variables. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer).” Authors should define how they measured race or ethnicity and justify their relevance.

ii. Technical Information

Specify the study's main and secondary objectives–usually identified as primary and secondary outcomes. Identify methods, equipment (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descrip¬tions for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. Identify appropriate scientific names and gene names.

iii. Statistics

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of mea¬surement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as P values, which fail to convey important information about effect size and precision of estimates. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

e. Results

Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods Section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

Give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to ta¬bles with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as “random” (which implies a randomizing device), “normal,” “significant,” “correlations,” and “sample.”

Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

f. Discussion

Emphasize the new and important aspects of the study and the conclusions that follow from them in the context of the totality of the best available evidence. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section. For experimental studies, it is useful to begin the discussion by briefly summarizing the main findings, then explore possible mechanisms or explanations for these findings, compare and contrast the results with other relevant studies, state the limitations of the study, and explore the implications of the findings for future research and for clinical practice.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when war¬ranted, but label them clearly.

g. References

i. General Considerations Related to References

Authors should provide direct references to original research sources whenever possible. Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

Do not use conference abstracts as references: they can be cited in the text, in parentheses, but not as page footnotes. References to papers accepted but not yet published should be designated as “in press” or “forthcoming.” Information from manuscripts submitted but not accepted should be cited in the text as “unpublished observations” with written permission from the source.

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References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses.

References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals). Journals vary on whether they ask authors to cite electronic references within parentheses in the text or in numbered references following the text. Authors should consult with the journal to which they plan to submit their work.

ii. Reference Style and Format

References should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Sample References webpage and detailed in the NLM's Citing Medicine, 2nd edition. These resources are

regularly updated as new media develop, and currently include guidance for print documents; unpublished material; audio and visual media; material on CD-ROM, DVD, or disk; and material on the Internet.

h. Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

Prepare tables according to the specific journal's requirements; to avoid errors it is best if tables can be directly imported into the journal's publication software. Number tables consecutively in the order of their first citation in the text and supply a title for each. Titles in tables should be short but self-explanatory, containing information that allows readers to understand the table's content without having to go back to the text. Be sure that each table is cited in the text.

Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes, and use symbols to explain information if needed. Symbols may vary from journal to journal (alphabet letter or such symbols as *, †, ‡, §), so check each journal's instructions for authors for required practice. Identify statistical measures of variations, such as standard deviation and standard error of the mean.

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Additional tables containing backup data too extensive to publish in print may be appropriate for publication in the electronic version of the journal, deposited with an archival service, or made available to readers directly by the authors. An appropriate statement should be added to the text to inform readers that this additional information is available and where it is located. Submit such tables for consideration with the paper so that they will be available to the peer reviewers.

i. Illustrations (Figures)

Digital images of manuscript illustrations should be submitted in a suitable format for print publication. Most submission systems have detailed instructions on the quality of images and check them after manuscript upload. For print submissions, figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints.

For X-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, send high-resolution photographic image files. Since blots are used as primary evidence in many scientific articles, editors may require deposition of the original photographs of blots on the journal's website.

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Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background. Explain the internal scale and identify the method of staining in photomicrographs.

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Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal.

Journals vary in the units they use for reporting hematologic, clinical chemistry, and other measurements. Authors must consult the Information for Authors of the particular journal and should report laboratory information in both local and International System of Units (SI).

Editors may request that authors add alternative or non-SI units, since SI units are not universally used. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

k. Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

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