DOES THE OVERALL DELAY BEFORE SURGERY AFFECT THE OUTCOME OF APPENDICITIS?

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DECLARATION

I, Farhana Jassat, (student number 0702595F) hereby declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine (Surgery), at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Signature: 

Date: 10/02/2023

Place: Parktown, Johannesburg

This report was written according to the guidelines of the South African Journal of Surgery (http://sajs.redbricklibrary.com/index.php/sajs/about/submissions) and is submitted in the submissible format of MMED reports as recognised by the Faculty of Health Sciences of the University of the Witwatersrand.

DEDICATION

This is dedicated to my family, for their unwavering support and encouragement.

ETHICAL CONSIDERATIONS

Permission for this retrospective study was obtained from the following administrators of Sebokeng Regional Hospital: Dr Nomsa Msibi, the acting CEO and from Mrs Dimakatso Radebe, the Laboratory Manager of the National Health Laboratory Service.

Ethics clearance was obtained from the Human Research Ethics Committee (HREC) (medical) of the University of the Witwatersrand (Clearance number – M190622).

ABSTRACT

Background: Surgery without delay has been the standard of treatment for acute appendicitis. Numerous studies have challenged this practice by defining a time frame for safely delaying surgery.

Objectives: To determine the effect of pre- and in-hospital delay on the outcome for patients with clinically acute unperforated appendicitis.

Methods: A single centre, retrospective two year descriptive study was undertaken at a regional hospital. Descriptive statistics were used to describe the patient population, pre- and in-hospital delay and surgical outcomes namely, severity of appendicitis, morbidity and length of hospital stay. Univariable and multivariable poisson regression with robust error variance was used to determine factors associated with suppurative or gangrenous appendicitis.

Results: 103 patients were included. The median age was 25 years (Inter Quartile Range 21-33 years) and 60 (58%) were male. The median pre-hospital delay was 48 hours (24-72 hours), in-hospital delay was 16.1 hours (9.5-22.5 hours) and overall delay was 56.3 hours (40.9-870 hours). There were no statistical differences between overall delay before surgery and surgical outcome. Pre-hospital delay was associated with findings of suppurative/ gangrenous appendicitis (p=0.032), post-operative complications (p=0.002) and longer hospital stays (Median 4 days (Inter Quartile Range 3- 6 days). Age (adjusted relative risk 1.34 (95% Confidence interval [0.99,1.80]) and white cell count (adjusted relative risk 1.55 (95% Confidence interval [1.09,2.20]) independently predicted adverse outcomes.

Conclusion: The overall delay before surgery does not affect the outcome of acute appendicitis. However, patients older than 25 years, with a pre-hospital delay of >2 days and a white cell count ≥11 cells/µl on presentation should be fast-tracked for surgery.

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LIST OF ABBREVIATIONS

AAST	**American Association for the Surgery of Trauma**
aRR	**Adjusted relative risk**
BP	**Blood pressure**
CI	**Confidence interval**
CRP	**C Reactive Protein**
CSMO	**Community service medical officer**
CT	**Computerized Tomography**
ED	**Emergency Department**
GIT	**Gastrointestinal Tract**
HREC	**Human Research Ethics Committee**
IQR	**Interquartile range**
LMIC	**Low and middle income**
LOS	**Length of stay**
MO	**Medical officer**
NHLS	**National Health Laboratory Service**
PE	**Pulmonary Embolism**
PR	**Pulse rate**
RIF	**Right iliac fossa**
RR	**Respiratory rate**
RVD	**Retroviral Disease**
SSI	**Surgical Site Infection**
US	**Ultrasound**
WCC	**White cell count**

INTRODUCTION

Background

Acute appendicitis is a common surgical condition and one that impacts on the global burden of surgical disease.[1] It has been almost 120 years since Dr Reginald Fitz, a Harvard pathologist and internist, first described the relationship between acute appendicitis or 'right iliac passions' as it was previously known and perforation. Since then, extensive research has been published on the topic in an attempt to refine the diagnosis, investigations and management of the condition with an ultimate aim of improving patient outcomes.[2]

Traditionally the concern was that every case of appendicitis, if surgical intervention was delayed, would invariably progress to complicated appendicitis. This view led to the move to emergency surgery immediately after the diagnosis of acute appendicitis was made . As a result, a certain rate of negative explorations for suspected appendicitis was regarded as acceptable surgical practice.[3] While there is no doubt that patients presenting with complicated appendicitis , peritonitis, or septic shock require urgent surgery for source control, a survey of the literature revealed that successful trials of short in-hospital delays prior to surgery for uncomplicated appendicitis is a valid option.[4]

The diagnosis of appendicitis relies on a thorough history, a good clinical examination supplemented with biochemical tests reflecting its inflammatory nature. The Alvarado score is a widely known, cost efficient scoring method used to assess the presence of acute appendicitis.[5] This is especially useful in a resource constrained environment where access to imaging modalities to confirm the diagnosis is not always possible.

In an effort to standardize the determination of disease severity, the American Association for the Surgery of Trauma (AAST) has developed an anatomic severity grading system. Higher scores were noted to be associated with open procedures, complications and length of hospital stay[6] For the purposes of this study, patients were classified as having either a mild appendicitis (AAST I), gangrenous appendicitis (AAST II) or locally perforated appendicitis (AAST III+IV).

The aim of this study was to determine the effect of pre- and in-hospital delay on the outcome for patients with clinically acute unperforated appendicitis. This in turn would determine if our

data is in keeping with international studies suggesting that ‘semi elective’ appendicectomies for uncomplicated appendicitis in a feasible option.

METHODS

Study Design

This was a retrospective descriptive cohort study based on record review conducted at Sebokeng Regional Hospital.

Study Setting

Sebokeng Regional Hospital is regional public sector hospital based in the Vaal Triangle, Gauteng Province, South Africa. It provides services to a catchment population of about 1 125 207 people. It comprises of a fully functional surgical department. The staff complement includes surgical consultants, medical officers (MO), community service medical officers (CSMO) and interns. Two surgical registrars affiliated to the University of the Witwatersrand rotate through the department on a four monthly basis as part of their surgical training. At the time this study was conducted, a 24-hour emergency theatre was available. No access to abdominal ultrasound (US) or computerized tomography (CT) scans were available after hours. Data was collected over a two year period from 1st January 2017 to 31 December 2018.

Inclusion and exclusion criteria

All male and female patients above and including the age of 18 years, identified from the emergency surgery record database as having undergone either a laparoscopic or open appendicectomy for uncomplicated appendicitis were included. Patients having undergone an exploratory laparotomy for suspected perforated appendicitis as well as missing patient files were excluded from the outset.

Relevant defining criteria

Unperforated acute appendicitis was defined as patients presenting with localized right iliac fossa (RIF) pain, localized tenderness or rebound tenderness on clinical examination without generalized peritonitis or a right iliac fossa mass (suspicious for an appendiceal mass

Symptom onset was defined as when the patient first noted the most discerning feature of acute appendicitis, being abdominal pain. Pre-hospital delay was defined as the patient's duration of symptoms from onset until presentation to hospital. In-hospital delay was divided into three categories namely: time from presentation to hospital until assessment by the emergency department (ED) casualty officer, time taken to be assessed by the surgeon on call and time from the decision to operate until surgery.

Study procedures

Patients were identified from the emergency surgery record database stored in the theatre recovery room. All patients who had undergone an appendicectomy (laparoscopic or open) were identified. A list of these patients were taken to the general filing department to obtain the patients' hospital files. The 'Patient Information Collection Sheet' designed by the primary investigator was used to collect all relevant information. Data was retrospectively captured for patient demographics, symptoms, duration of symptoms, time at which the patient was assessed by the emergency department casualty officer, assessed by the surgeon and ultimately time to surgery in hours. The surgeon's intraoperative findings were recorded. Additional haematological, microbiological, and histological results were obtained from the National Health Laboratory Services (NHLS) Track Care database. Patient files were used to track the patient's post-operative course, to assess for the development of complications, in-hospital mortality and to determine the total length of stay up until discharge. Data was entered in an Excel 2007 datasheet (Microsoft, USA). This document was password protected and access was strictly guarded. Patient confidentiality was maintained by assigning a study number to each identified case.

Statistical analysis

Stata version 13.1 was used for statistical analysis. Descriptive statistics were used to describe the patient population, pre- and in-hospital delay and surgical outcomes namely, severity of appendicitis, morbidity and length of hospital stay. Univariable and multivariable poisson regression with robust error variance was used to determine factors associated with suppurative or gangrenous appendicitis. A p value of <0.05 was considered statistically significant. Factors

which had a p-value of <0.2 in the univariable analyses were included in the multivariable model.

Ethics

Ethics clearance was obtained from the Human Research Ethics Committee (HREC) (medical) of the University of the Witwatersrand (Clearance number – M190622).

RESULTS

Description of included patients

A total of 182 patients were identified from the theatre record books as having undergone an open or laparoscopic appendicectomy during the two year study period. Of these, 79 (43%) patients were excluded from the analysis as 34 (18%) patients had missing files, 29 (16%) patients had a histologically normal appendix and 16 (9%) patients had an alternate diagnosis involving the appendix. The median age of the 103 (57%) patients who were included was 25 years (Inter Quartile Range [IQR] 21-33 years), 60 (58%) were male and 92 (89%) were of African descent. Eighty six (83%) patients had no medical comorbidities. All 103 (57%) patients had an Alvarado score of >7. The median white cell count (WCC) was 13 cells/ul (IQR 10-17 cells/ul).

Pre- and in-hospital delay and surgical outcome

The median pre-hospital delay was 48 hours (IQR 24-72 hours), time from presentation to hospital until assessment by the emergency department casualty officer 1.33 hours (IQR 0.25 – 2.5 hours), time to be assessed by the surgeon on call 2.33 hours (IQR 1.50 – 4.17 hours) and time from the decision to operate to surgery 10 hours (IQR 5.50 – 16.33 hours) (Table 1). All intraoperative appendix specimens were evaluated by a pathologist. Thirty six (35%) patients had mild appendicitis, 25 (24%) patients had gangrenous appendicitis and 42 (41%) patients had suppurative appendicitis. There were no statistical differences in the overall delay before surgery with the histological findings. However, differences existed in the pre-hospital delay when comparing the mild appendicitis group *vs* the suppurative/gangrenous appendicitis group. Pre-hospital delay was longer among the suppurative/gangrenous appendicitis group compared with the mild appendicitis group (Median 48 hours *vs* 24 hours) (p=0.032) (Table 2). Patients who developed post-operative morbidity were taken to theatre much sooner than those who did not (p=0.089). There were no mortalities among the included patients. Post-operative complications were classified according the to the Clavien Dindo Classification system (Figure 1). A pre-hospital delay of two days was associated with post-operative morbidity (p=0.002) (Table 3). Thirty five (34%) patients developed morbidity, all of them arising from patients found to have suppurative/ gangrenous appendicitis. Of the 67 (65%) patients found to have suppurative/gangrenous appendicitis, 32 (47%) patients did not develop any complications.

From the 35 (53%) patients that did develop morbidity, 20 (29.9%) patients developed surgical site infection with intra-abdominal collections requiring a relook laparotomy and 11 (16.4%) patients developed a post-operative ileus (Table 4). The median length of stay for patients with mild appendicitis was 1(IQR 1-2) day and for patients with suppurative/gangrenous appendicitis 4 (IQR 3-6) days ($p<0.001$).

Factors associated with suppurative/gangrenous appendicitis

Univariable and multivariable poisson regression analysis showed that the overall delay before surgery was not associated with suppurative/gangrenous appendicitis. However, age and white cell count were identified as independent predictors of suppurative/ gangrenous appendicitis (Table 5). A white cell count of ≥11cells/ul was associated with a 55% higher risk of suppurative/ gangrenous appendicitis (adjusted relative risk (aRR) 1.55 [95% confidence interval (CI) [1.09,2.20] ($p=0.016$) compared to a low/ normal white cell count while there was a trend towards higher risk of suppurative/gangrenous appendicitis with age older than 25 years (adjusted relative risk (aRR) 1.34 [95% confidence interval (CI) [0.99,1.80] ($p=0.052$). Higher pre-operative temperatures and C-reactive protein levels were not associated with an increased risk of suppurative/gangrenous appendicitis.

DISCUSSION

Acute appendicitis affects both genders, does not discriminate between race and affects both young and old. Its incidence peaks in children and young adults.[7] This is depicted in our study as 71% of patients were in the age range of 18-30 years. Most patients were of African descent (89%) reflecting the profile of patients presenting to Sebokeng Regional Hospital and in our South African context. A study conducted by Kong *et al.,* at another busy regional hospital in South Africa reflected similar demographic findings.[8]

The main pathogenic trigger implicated in acute appendicitis is obstruction of the appendicular lumen. Obstruction leads to inflammation. Stasis in the lumen allows intestinal bacteria to multiply, recruiting white blood cells and accumulating purulent material. Obstruction causes the intraluminal pressure to rise, resulting in wall ischaemia, necrosis and eventual rupture.[7] There is no doubt that if this process is left untreated, progressive inflammation from this seemingly benign appendage will result in disastrous consequences. This is directly related to the development of complicated intra-abdominal infection such as intra-abdominal abscesses or purulent peritonitis, a process that is time dependent and one that requires prompt source control to avoid significant morbidity and mortality.[9]

Performing an appendicectomy is considered the bread and butter of any surgeon's armamentarium. However, the timing of surgery and the effect of delays thereof has remained a contentious issue in the literature over the years. This study demonstrated that whilst overall delay before surgery i.e. encompassing both pre- and in-hospital delay did not affect the outcome of acute appendicitis, pre-hospital delay was identified as a significant factor implicated in both disease severity and patient outcome.

Pre-hospital delay

Making contact with a health care system is referred to as health seeking behaviour (HSB). It is defined as "any action or inaction undertaken by individuals who perceive themselves to have a health problem or to be ill for the purpose of finding an appropriate remedy".[10]

In our study, it appears that delay in seeking medical attention is a predictor of poorer outcome rather than in-hospital delay. Patients with a pre-hospital delay of greater or more than 2 days were more likely to have suppurative/gangrenous appendicitis as well as develop post-operative morbidity. Thus, an important conclusion drawn from these findings is that patients with pre-hospital delay of > two days should be fast tracked for surgery. Similar to our findings, a study conducted in a resource constrained tertiary centre in Malawi showed that whilst delays in accessing health care did not directly increase the risk of mortality, it was an important factor driving non-fatal complications.[11]

TABLE 1. Analysis of overall delay before surgery (N=103)

Time period	**Median (IQR)**
Pre-hospital delay (in hours)	
Onset of symptoms to presentation	48 (24 – 72)
In hospital delay (in hours)	
Presentation to casualty officer	1.33 (0.25 – 2.5)
Casualty officer to surgeon	2.33 (1.50 – 4.17)
Surgeon to surgery	10 (5.50 – 16.33)
Overall hospital delay	15.75 (9.5 – 22.42)
Total delay (in days)	2.46 (1.70 – 3.58)

TABLE 2. Analysis of association between overall delay before surgery and the histology/pathology of the appendix (N=103)

Time period	**Early mild Appendicitis** Median (IQR)	**Gangrenous/ suppurative** Median (IQR)	**P value (Wilcoxon Ranksum test)**
Duration of symptoms (in hours)	24 (24 – 48)	48 (24 – 72)	**0.032**
Presentation to casualty officer (hours)	1.5 (0.54 – 2.08)	1.25 (0 – 2.5)	0.770
Casualty officer to surgeon (hours)	2 (1.12 – 4.50)	2.5 (1.5 – 4.0)	0.675
Surgeon to surgery (hours)	13.25 (6.5 – 19.17)	9.42 (5.33 – 15.17)	**0.089**
Overall hospital delay (hours)	19.33 (10.04 – 23.83)	13.83 (8.83 – 20.17)	0.145
Total delay (in days)	1.99 (1.76 – 3.01)	2.58 (1.67 – 3.91)	0.120

TABLE 3. Association of overall delay before surgery and morbidity

Time period	No post-op morbidity	Post-op morbidity	P value
Onset of symptoms to presentation (hours)	24 (24 – 48)	48 (24 – 96)	**0.002**
Presentation to casualty officer (hours)	1.08 (0.21 – 2.08)	2 (0.25 – 2.75)	0.244
Casualty officer to surgeon (hours)	2.33 (1.5 – 4.08)	2.33 (1.5 – 4.33)	0.884
Surgeon to surgery (hours)	11.54 (6.5 – 17.96)	7.33 (4.83 – 15.17)	0.030
Overall hospital delay (hours)	16.62 (10.75 – 23.62)	13.83 (8.0 – 19.17)	0.123
Total delay (in days)	2.09 (1.62 – 3.06)	2.80 (2.14 – 4.35)	0.056

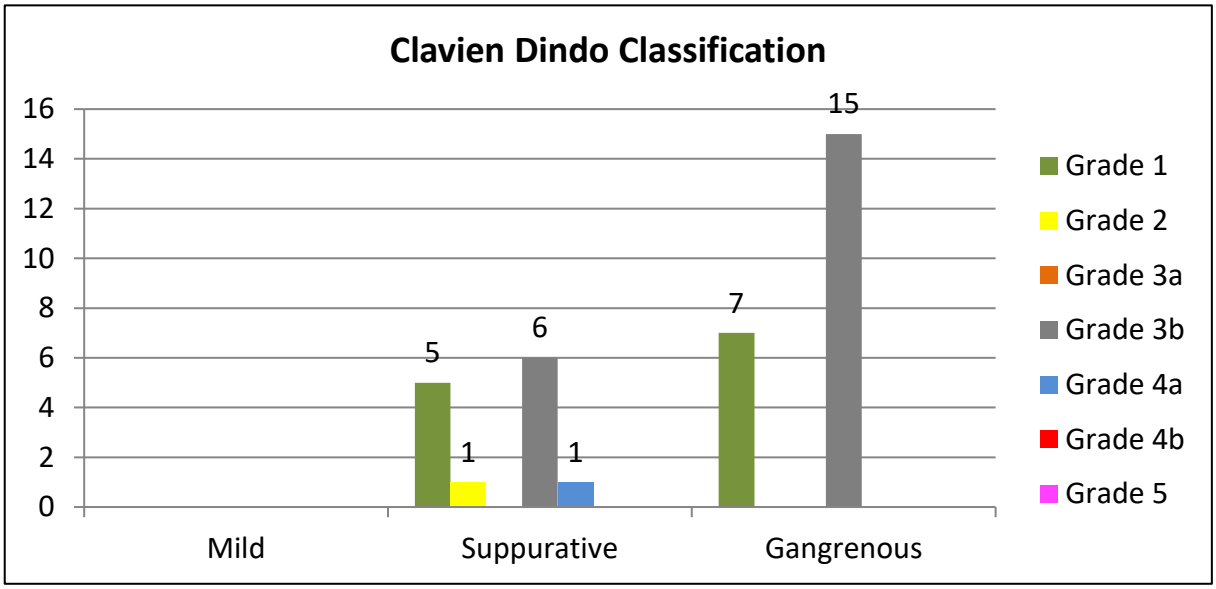

FIGURE 1.Clavien Dindo Classification of post-operative morbidity for mild, suppurative and gangrenous appendicitis.

The commonest post-operative complication identified in our cohort of patients with suppurative/gangrenous appendicitis was surgical site infection with underlying intra-

abdominal collections. Surgical site infection or the development of intra-abdominal collections is not a surprising finding and speaks to the progressive nature of the disease and the importance of source control in complicated appendicitis.

TABLE 4. Type of complications in patients with suppurative/gangrenous appendicitis.

Type of complication in patients with suppurative/ gangrenous appendicitis	N	%
Grade 1- Ileus	11	16.4
Grade 1- Wound sepsis managed with dressings	1	1.5
Grade 2- Aspiration pneumonia	1	1.5
Grade 3b- Iatrogenic bowel injury	1	1.5
Grade 3b- Surgical site infection- relook and washout for collections	20	29.9
Grade 4a- PE, Biventricular failure	1	1.5
None	32	47.8

No mortalities were reported in our cohort of patients. A possible reason for this could be that critically ill patients presenting with features of complicated appendicitis such as generalized peritonitis or septic shock were taken to theatre for an emergency laparotomy. These patients were excluded from our study from the outset.

Delays in seeking access to medical care is an issue that is not unique to our patient population. A study conducted by Kong *et al.,* looked at the reasons for delay to definitive surgical care in a cohort of patients in rural South Africa. The authors found that there was a >48 hour delay in 70% of patients presenting with acute appendicitis.[12] Another local study by Yang *et al.,* compared patients with acute appendicitis in both the private and public health sectors in Cape Town, South Africa. Surprisingly, they concluded that pre-hospital delays were comparable at 49 and 56 hours respectively.[13]

There are a number of factors that could be implicated in delays to seeking medical care. South Africa, as a low and middle income country (LMIC), has a social environment and population demography uniquely different from high income countries. In addition, disparities between urban and rural based patients seeking medical care as well as differences between private and

public sector hospitals within our country exist. The former was highlighted by a study conducted in Pietermaritzburg that identified rural origin as an independent predictor of worse outcomes in acute appendicitis.[14] Unfortunately, a significant limitation to our study was its retrospective nature. Hence, reasons that deterred health seeking behaviour in our patient cohort could not be determined. Important barriers to health care could be extrapolated from other countries with similar social standing.[15,16]

In-hospital delay

Reasons for in-hospital delays prior to surgery are multifactorial. The use of an effective triage system, the efficiency and staffing of the ED, the number of surgical doctors on call, their work load, availability of radiological services as well as access to a 24 hour emergency operating theatre, amongst others play a pivotal role. A Sudanese study found that the misdiagnosis of acute appendicitis in 65% of their study sample contributed the greatest reason for in-hospital delay.[17]

In our cohort of patients, in-hospital delay was divided into three categories namely; time from presentation to hospital until assessment by the casualty officer, the time taken to be assessed by the surgeon on call and lastly, the time from the decision to operate to surgery. Whilst none of these categories reached statistical significance, a few observations could be drawn. The median delay for each of the three categories were 1 hour, 2 hours and 10 hours respectively. The ED is generally better staffed and patients tend to be assessed much quicker. Longer delays to surgery after being diagnosed with acute appendicitis by the surgeon on call could be explained by the fact that there was only one senior surgeon on call every night assisted by junior staff comprising of interns or CSMOs. This team was responsible for dealing with all new surgical emergencies as well as tending to critically ill surgical in-patients. It was thus the prerogative of the surgeon on call to triage all cases awaiting theatre. One could assume that critically ill patients, after a period of adequate resuscitation, were prioritized above more stable patients. However, what did reach statistical significance, was that patients retrospectively found to have suppurative or gangrenous appendicitis, were taken to theatre much sooner. Thus, one could postulate that the surgeon acted quicker for sicker patients.

This retrospective study did not find that the overall in-hospital delay affected the outcome of acute appendicitis. Importantly, international literature reflects otherwise. In a large multicentre cohort study, systematic review and meta-analysis conducted by Bhangu *et al.*, the main finding of both the cohort and meta-analysis phase was that a short delay of 12-24 hours was not associated with an increased risk of complex appendicitis. In addition, short delays were not associated with increased rates of infectious complications. What the cohort study did show was that delays beyond 48 hours were associated with an increased risk of wound infection without a risk of perforation. The investigators suggested that short in-hospital delays are indeed a safe option especially with intravenous antibiotics and fluid resuscitation on-board, but that prompt surgery (if resources allow) should still be undertaken to allow faster resolution of patient symptoms.[18] Another meta-analysis conducted by van Dijk *et al.*, demonstrated that a delay of up to 24 hours post-admission for suspected uncomplicated acute appendicitis was not a risk factor for complicated appendicitis, post-operative surgical site infection or morbidity.[4]

Whilst emergency surgery is a life-saving necessity, it is not without its drawbacks.[4] Safely delaying appendicectomies for daylight hours, had our study concluded as such, could have had considerable benefits in our setting. Our health care system is crippled with numerous challenges ranging from lack of equipment, dire staff shortages, and at times, insufficient senior supervision.[19,20] Daytime operating would enhance the training of junior surgeons and improve patient outcomes as compared to night time emergency operations performed by sleep deprived trainees often without supervision.[18] A safe time frame for delaying appendicectomies in our setting could not be determined. A possible reason for this could be that this was a single centre retrospective study conducted at a regional hospital with a small sample size. Thus, a greater number of hospitals with a larger pool of patients could be a better representation when answering this objective.

Predictors of suppurative and gangrenous appendicitis

Our study found that age and WCC were independent predictors of gangrenous and suppurative appendicitis. A study by Nomura *et al.*, also identified age as a risk factor, since aging is associated with compromised immunity and more severe inflammation.[21] However, since a

minority of our patient cohort were above 41 years of age, extremes of age could not be implicated in this process. Numerous studies have also alluded to the role serum bilirubin plays as a predictor of complicated appendicitis.[22,23] In our study, the diagnosis of appendicitis was made using the Alvarado score, which requires the WCC and left shift only. Liver function tests were not regarded as a standard biochemical investigation for purposes of making a diagnosis. It would however be an interesting study to conduct in our setting, to see if serum bilirubin levels predict complicated appendicitis.

TABLE 5. Factors associated with suppurative/gangrenous appendicitis

Variable	% with suppurative/ gangrenous appendicitis	Univariable Relative risk (RR) 95% CI	p-value	Multivariable Relative risk (RR) 95% CI	p-value
Age (years)					
<25	26/49 (53.1)	1.00		1.00	
≥25	41/54 (75.9)	1.43 (1.06- 1.94)	0.021	1.34 (0.99- 1.80)	0.054
Temperature (°C)					
<37	62/97 (63.9)	1.00		1.00	
≥37	5/6 (83.3)	1.30 (0.88- 1.93)	0.182	1.00 (0.69- 1.47)	0.989
Total delay (hours)					
<48	24/44 (54.6)	1.00		1.00	
48- 72	18/25 (72.0)	1.32 (0.92-1.90)	0.137	1.32 (0.92- 1.90)	0.129
72- 96	8/14 (57.1)	1.05 (0.62- 1.78)	0.864	1.02 (0.64- 1.62)	0.931
>=96	17/20 (85.0)	1.56 (1.12- 2.16)	0.084	1.28 (0.92- 1.77)	0.139
White cell count (cells/µL)					
<11 cells/µl	19/42 (45.2)	1.00		1.00	
≥11 cells/µl	48/61 (78.7)	1.74 (1.21- 2.49)	0.003	1.55 (1.09- 2.20)	**0.016**
C-reactive protein (mgl/L)					
<10	9/25 (36.0)	1.00		1.00	
10- 50	12/21 (57.1)	1.59 (0.83- 3.02)	0.159	1.26 (0.67- 2.37)	0.471
≥50	46/57 (80.7)	2.24 (1.31- 3.85)	0.003	1.61 (0.90- 2.86)	0.109

Study limitations

This study has several limitations. Firstly, limited control could be exercised over meticulous record keeping as it was a retrospective study. This could have resulted in substantial recall bias. Secondly, the generalizability of the results is limited as our study was conducted at a single institution and this may not be representative of our local data. Thirdly, this study was conducted at a regional training hospital and it is therefore uncertain whether such findings

could be extrapolated to the tertiary level teaching hospitals that have a larger and more senior staff complement with more supervision. Lastly, many patients were excluded from this study due to missing patient files. This greatly impacted on the sample size and could have resulted in a potential bias.

CONCLUSION

Pre-hospital rather than overall delay affected the outcome of acute appendicitis. It was determined that patients older than 25 years, with a pre-hospital delay of > 2 days and a white cell count ≥11 cells/µl on presentation should be fast-tracked for surgery.

RECOMMENDATIONS

Initiatives aimed at improving access to health care is imperative. Patient education about the signs and symptoms of acute appendicitis to ensure prompt recognition to spur health seeking behavior should be a cornerstone in this endevour. In addition, public health and sociological research encompassing a greater number of hospitals with a larger sample size would provide valuable information required to improve our understanding of the reasons for late presentation in our setting.

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APPENDICES

APPENDIX 1: Protocol

1. INTRODUCTION AND LITERATURE REVIEW

Acute appendicitis is a common surgical condition and one that impacts on the global burden of surgical disease (Ferris *et al*., 2017). It has been almost 120 years since Dr Reginald Fitz, a Harvard pathologist and internist, first described the relationship between acute appendicitis or 'right iliac passions' as it was previously known and perforation. Since then, extensive research has been published on the topic in an attempt to refine the diagnosis, investigations and management of the condition with an ultimate aim of improving patient outcomes (Evans, 2006).

Historically speaking, acute appendicitis has always been regarded as a disease that constituted a surgical emergency and subsequently one that required *urgent* surgical removal for definitive cure (Eko *et al*., 2013). This has been the standard treatment of care in the last century (Shin *et al*., 2014).

This aggressive surgical policy of early intervention by surgeons when the diagnosis is suspected, most likely stems from the belief that inflammatory appendicitis is a progressive disease (Drake *et al*., 2014). This view emanates from the conventional pathophysiologic model of acute appendicitis, which is based on a relationship between time and disease progression. Thus, any delay in surgery was believed to result in an acute uncomplicated inflamed appendix progressing to necrosis and perforation (Fitz, 1886).

Whilst it is universally accepted that if left untreated, acute appendicitis may have dire consequences, the resort to emergency surgery for appendicitis has in recent years been challenged by numerous studies, which have focussed on defining a safe time frame by which

surgery for acute appendicitis can be delayed without any increase in morbidity (van Dijk *et al*., 2018). The foundation for this is perhaps based on a new pathophysiologic model which has demonstrated the possibility that perforated and non- perforated appendicitis may be fundamentally different disease processes. Hence, not all cases of acute appendicitis not treated by surgery will perforate (Livingston *et al*., 2007).

Anatomy and function

The appendix or vermiform appendix (derived from the Latin word meaning 'worm-like') is a blind ending tubular structure that forms part of the digestive tract. Although the exact function of the appendix is unknown, the presence of lymphatic tissue in it suggests a role of the appendix in the immune system. The appendix forms during embryological development from the posteromedial wall of the caecum approximately 2 cm below the ileocaecal valve. It derives its blood supply from the appendicular artery which is a terminal branch of the ileocolic artery (Martin, 2018).

Though the attachment of the appendix to the caecum is constant, the migration of its tip may result in normal anatomical variations namely, retrocaecal, paracolic, subcaecal, preileal, postileal, and pelvic positions (Ghorbani *et al*., 2014).

Since acute appendicitis is generally regarded as a clinical diagnosis, these anatomical variations are of great significance. It may provide a challenge to the examining surgeon who may be misled in arriving at an alternate or incorrect diagnosis (Ghorbani *et al*., 2014).

Epidemiology and incidence

Acute appendicitis is a global disease (Ferris *et al*., 2017). It affects both genders, does not discriminate between races and affects both young and old. Its incidence peaks in children and young adults (Yang *et al*., 2015).

A systematic review that had examined literature on acute appendicitis in South Africa, showed that the incidence rate in White South Africans was comparable to that of developed countries, whereas the incidence in Black South Africans was significantly lower. This, in addition to high perforation rates of 36% was largely attributed to a delay in seeking medical care (Yang *et al*., 2015).

Women were noted to have had a higher negative operation rate compared to men. Men were more likely to have more serious disease. This review also implicated perforation and generalised peritonitis as the cause of nearly all deaths recorded in patients who had undergone appendectomies (Yang *et al*., 2015).

The pathogenesis of acute appendicitis

The main pathogenic trigger implicated in acute appendicitis is believed to be an obstruction of the appendicular lumen (Yang *et al*., 2015). This obstruction may result from several causes, including faecoliths, lymphoid hyperplasia, foreign bodies, parasites as well as primary and metastatic tumours.

Obstruction leads to inflammation. Stasis in the lumen allows intestinal bacteria to multiply, recruiting white blood cells and accumulating purulent material. This causes the intraluminal pressure to rise, resulting in wall ischaemia, necrosis and eventual rupture (Yang *et al*., 2015).

The acute inflammation of appendicitis may be classified as uncomplicated or complicated appendicitis. Uncomplicated appendicitis refers to an inflamed appendix without gangrene,

perforation or a surrounding abscess. Complicated appendicitis refers to a gangrenous, perforated appendix or the presence of an appendicular abscess.

Safety of appropriate in hospital delay

Traditionally the concern was that every case of appendicitis, if surgical intervention was delayed, would invariably progress to complicated appendicitis. This view led to the move to emergency surgery immediately after the diagnosis of acute appendicitis was made (Fitz, 1886). As a result, a certain rate of negative explorations for suspected appendicitis was regarded as acceptable surgical practice (Livingston *et al*., 2007).

While there is no doubt that patients presenting with complicated appendicitis , peritonitis, or septic shock require urgent surgery for source control, a survey of the literature revealed that successful trials of short in-hospital delays prior to surgery for uncomplicated appendicitis is a valid option (van Dijk *et al*., 2018).

In a large multicentre cohort study, systematic review and meta-analysis conducted by Bhangu *et al.,* the main finding of both the cohort and meta-analysis phase of this study was that a short delay of 12-24 hours was not associated with an increased risk of complex appendicitis. In addition, the meta-analysis showed that these short delays were not associated with increased rates of infectious complications. The cohort study showed that delays beyond 48 hours were associated with an increased risk of wound infection without a risk of perforation. The investigators suggest that short in-hospital delays are indeed a safe option especially with intravenous antibiotics and fluid resuscitation on-board, but that prompt surgery (if resources allow) should still be undertaken to allow faster resolution of patient symptoms (Bhangu *et al*., 2014).

In the most recent meta-analysis conducted by van Dijk *et al.*, databases on acute appendicitis from 1990 to 2016 were examined. It involved 152 314 patients and demonstrated that a delay of up to 24 hours post admission for suspected uncomplicated acute appendicitis was not a risk factor for complicated appendicitis, post-operative surgical site infection or morbidity (van Dijk *et al*., 2018).

Benefits of delay

Whilst emergency surgery is a life-saving necessity, it is not without its drawbacks. In addition, operating during the night also lends itself to higher morbidity and error rates (van Dijk *et al*., 2018).

Whilst most regional and tertiary hospitals in South Africa provide 24 hour operating room facilities, safely delaying appendicectomies for daylight hours may have considerable benefits. Daytime operating will enhance the training of junior surgeons and improve patient outcomes as compared to night time emergency operations performed by sleep deprived trainees often without supervision (Bhangu *et al*., 2014). In Sebokeng Regional Hospital, the availability of laparoscopy as well as imaging modalities such as an abdominal ultrasound and computed tomography are available only during the daytime and this may reduce negative appendicectomy rates.

What about pre-hospital delay?

Delays may occur at any point from symptom onset to treatment and contributory factors include aspects of the disease itself, patient characteristics, access to medical care as well as the efficiency of the health care system (Drake *et al*., 2014).

It is difficult to analyze the patient's pre-hospital delay in order to establish the precise time of symptom onset. Factors such as recall bias or poor time discrimination may hamper objective collection of data for the study (Drake *et al*., 2014).

Bearing this in mind, a number of studies support the hypothesis that perforated complicated appendicitis is a separate disease entity rather than being the next stage of the natural course of the disease (Hornby *et al*., 2013).

The meta analysis conducted by van Dijk *et al.,* alluded to the fact that it is the disease itself that may lead to perforation instead of a delay in surgery. The implication of this is that most appendices will already have perforated on arrival and that perforation can thus not be prevented by urgent surgery (van Dijk *et al*., 2018).

South Africa, as a low and middle income country, has a social environment, health care system structure and population demography uniquely different from high income countries. In addition, our health care system is crippled with numerous challenges ranging from lack of equipment, dire staff shortages, and at times, insufficient senior supervision.

This study will thus determine if our local data is in keeping with data from high income countries which indicate that an appropriate delay before surgery for uncomplicated appendicitis is a safe and feasible option. If this is the case, surgery could be delayed for daylight hours, fresh staff and lighten the burden of the on-call staff without compromising patient outcome. If our data reflects otherwise, the historic practice of urgent emergency appendicectomies without delay should be continued in our setting.

2. AIMS AND OBJECTIVES

Aim

The aim of the study is to determine if surgery for patients presenting with acute unperforated appendicitis clinically, can be safely delayed for a short period without resulting in adverse outcomes.

Primary objectives

1. To analyse the time frame from onset of symptoms, presentation to hospital and time to theatre.
2. To determine if there is a correlation between the overall delay before surgery and the histological/ pathological state of the appendix.
3. To ascertain if the overall delay has any impact on post-operative morbidity, mortality and resource utilization of the health care institution.
4. To determine what constitutes a safe time frame in our setting for delaying appendicectomies for suspected unperforated acute appendicitis.

Secondary objectives

1. To determine if our local data is in keeping with international studies suggesting that 'semi elective' appendicectomies for uncomplicated acute appendicitis is indeed a feasible option.

3. METHODOLOGY

3.1 Study design

A single centre, retrospective descriptive study will be undertaken at Sebokeng Regional Hospital, which is a regional public sector hospital based in the Vaal Triangle, Gauteng Province, South Africa.

3.2 Study period

1st January 2017- 31 December 2018

3.3 Sample study/ participants

All patients including and above the age of 18 who had undergone a laparoscopic or open appendicectomy after being diagnosed as having acute appendicitis on presentation in the retrospective 24 month study period will be included in the sample study.

A quick review of the emergency theatre record books has indicated that on average, about 6 adult patients had undergone either an open or laparoscopic appendicectomy each month. With this in mind, it is assumed that such patients would have presented with suspected unperforated acute appendicitis to enable the attending surgeon to tackle the case in this manner without electing to proceed with an exploratory laparotomy. We estimate the sample size to average 140 patients and will meet the minimum required number of 100 patients for a retrospective study.

Relevant defining criteria

The diagnosis of acute appendicitis will be made using the Alvarado score. It is a widely known, cost efficient scoring method used to assess the presence of acute appendicitis. This is especially useful in a resource constraint environment where access to imaging modalities to confirm the diagnosis is limited and not always possible. Patients having undergone surgery will be assumed to have had an Alvarado score of >7.

Unperforated acute appendicitis will be defined as patients presenting with:

1. Localized right iliac fossa pain and
2. Localized tenderness or rebound tenderness on clinical examination
3. Without generalized peritonitis or a right iliac fossa mass (suspicious of an appendiceal mass).

Inclusion criteria

1. Male and female patients above and including the age of 18 years, identified from the theatre record book as having undergone either a laparoscopic or open appendicectomy.

Exclusion criteria

1. Patients identified retrospectively from the theatre record book as having undergone an exploratory laparotomy for suspected perforated appendicitis.
2. Patients with incomplete medical records.

a. Measuring tool/ Instrument

Patients will be identified from the emergency surgery record database stored in the theatre recovery room. All patients noted to have undergone an appendicecotmy (laparoscopic or open) will be recorded. A list of these patients will be taken to the general filing department to obtain the patients' hospital files. The in- patient hospital files will thus be the main source of information. Blood, microbiological and histological results will be obtained from the National Health Laboratory Service at Sebokeng Regional Hospital.

b. Data collection

Relevant information will be extracted from the patients file to complete the 'Patient Information Collection Sheet' designed by the primary investigator. See Appendix 1.

Data will then be transferred to an Excel 2007 datasheet (Microsoft, USA).This document will be password protected and access will be strictly guarded.

4.DATA ANALYSIS

The extracted data will be transferred to a Microsoft Excel 2007 (Microsoft,USA) spreadsheet for further analysis. Confidentiality will be maintained by assigning a study number to each identified case. Data will be analyzed using descriptive statistics as well as a chi-squared (χ^2)test for measures of association between the nominal data obtained. The variables will be plotted on a frequency graph. Normal distribution will be represented by means and standard deviations. Skewed distributions will be represented by medians and interquartile ranges. Outcomes will be analyzed using the students'*t*-test if the data is normally distributed. The Mann Whitney test will be used if the data is not normally distributed. A p value of <0.05 will be considered statistically significant.

5.ETHICS

Ethical clearance will be applied for from the University of the Witwatersrand Human Research Ethics Committee (HREC medical). Permission from the Chief Executive Officer of Sebokeng Regional Hospital will also be obtained by registering the research project on the National Health Research Database, for access to patient records and clinical data. Permission will be obtained from the National Health Laboratory Service based at Sebokeng Regional Hospital for access to haematological, microbiological and histological data.

6.TIMING

	2018	2019												2020		
Process	***Dec***	***Jan***	***Feb***	***Mar***	***Apr***	***May***	***Jun***	***July***	***Aug***	***Sept***	***Oct***	***Nov***	***Dec***	***Jan***	***Feb***	***Mar***
Project Idea	X															
Literature review		X														
Preparing protocol			X													
Protocol deadline				13 Mar												
Protocol assessment					10 Apr											
Ethics application						31 May										
Data collection							X	X	X							
Data analysis										X	X	X	X			
Report write up														X	X	
Report submission																X
Finalize/ submit publication																X

7.FUNDING

No significant financial implications are expected to be incurred from this study. Minor travelling costs to and from Sebokeng Regional Hospital will be covered by the primary investigator.

8.LIMITATIONS TO THE STUDY

Poor record keeping and missing patient documentation may pose a challenge. As patients with incomplete medical records will be excluded from the study, this will not only result in a reduction in sample size, but also result in a potential bias. The limitation with regards to sample size may be mitigated by increasing the study period. Should this be the case, a request of amendment of the protocol will be submitted to the University of the Witwatersrand Human Research Ethics Committee (HREC medical). The time period of the study will subsequently be amended pending ethics approval. Owing to the retrospective nature of this study, another potential limitation may be the inferior levels of evidence obtained as compared to a prospective study. The greatest limitation anticipated is the high likelihood of incomplete Alvarado score assessments made by the attending doctor when the patient presented to hospital.

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APPENDIX 2: Patient Information Collection Sheet

Patient Information Collection Sheet							
Patient details							
Study no							
Age	18-25	26-30	31-35	36-40	41-45	46-50	>50
Gender	Male	Female					
Ethnicity	African	Caucasian	Indian	Coloured	Asian		
History							
Presenting complaint	Migratory RIF pain	Anorexia	Nausea and vomiting	Fever	GIT symptoms Vomiting/ Diarrhoea	Urinary tract symptoms Frequency, urgency	Other symptoms
Duration of symptoms	< 1 day	1 day	2 days	3 days	4 days	5 days	>5 days
Reason for delay (if noted)	No transport	No money	Live too far	Family responsibility	Sought alternative treatment	Hoped it would get better	Other
Treatment commenced prior to arrival	Analgesia	Antibiotics	Herbal/ traditional	Other			
Co morbid conditions	RVD	Hypertension	Diabetes	Other			
Clinical examination							
Vital signs	BP	PR	RR	Temp			
Abdominal examination	Localised RIF tenderness	Rebound RIF tenderness	Generalised peritonitis	Appendiceal mass	Not convincing		

Investigations							
Urine dipstix	Y	N	Result				
Pregnancy test	Y	N	Result				
Blood tests	WCC	Left shift	CRP	PCT	Blood gas	None	
AXR	Y	N	Findings				
Diagnosis							
Level of experience	Intern	CSMO	Medical officer < 5 years	Medical officer >5 years	Junior Registrar	Senior registrar	Consultant
Diagnosis made	Clinically	Imaging CT/ U/S	Findings			Alvarado score:	
Management instituted on presentation at Sebokeng Hospital							
Antibiotics	Y	N					
Booked for theatre	Time of booking						
Evaluation of in hospital delay							
Time from presentation to hospital till time seen by the casualty officer					Arrival	Seen	Hours
Time referred by the casualty officer till time seen by the surgical team					Referred	Seen	Hours
Time seen by the surgical team till time of operation					Seen	Operation	Hours
Classification of overall in hospital delay					**Early <12 hours**	**Early delayed 12-24 hours**	**Delayed >24hours**
Intraoperatively							
Duration of operation:							

Operating surgeon	CSMO	Medical officer < 5 years	Medical officer > 5 years	Junior registrar	Senior Registrar	Consultant	
Surgical technique	Open	Laparoscopic	Conversion	Reason for conversion			
Intraoperative findings	Normal looking appendix	Oedema/ Hyperaemia	Fibrinous Exudate	Necrosis/ Perforation	Abscess/ localized peritonitis	Generalised peritonitis	Phlegmon
Histology	Lab sticker	Findings					
Microbiology	Lab sticker	Findings					
Postoperative course							
Duration of hospital stay							
Morbidity	Y- List the morbidity:			N			
Clavien Dindo classification	Grade I	Grade II	Grade IIIa	Grade IIIb	Grade IVa	Grade IVb	
	Grade V	Cause of death					

APPENDIX 3: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Farhana Jassat

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M190622

NAME: (Principal Investigator)	Dr Farhana Jassat
DEPARTMENT:	General Surgery Sebokeng Regional Hospital Vaal Triangle, Gauteng, South Africa
PROJECT TITLE:	Does the overall delay before surgery affect the outcome of acute appendicitis?
DATE CONSIDERED:	28/06/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Rachel Moore and Dr Marietha Nel
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	01/10/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

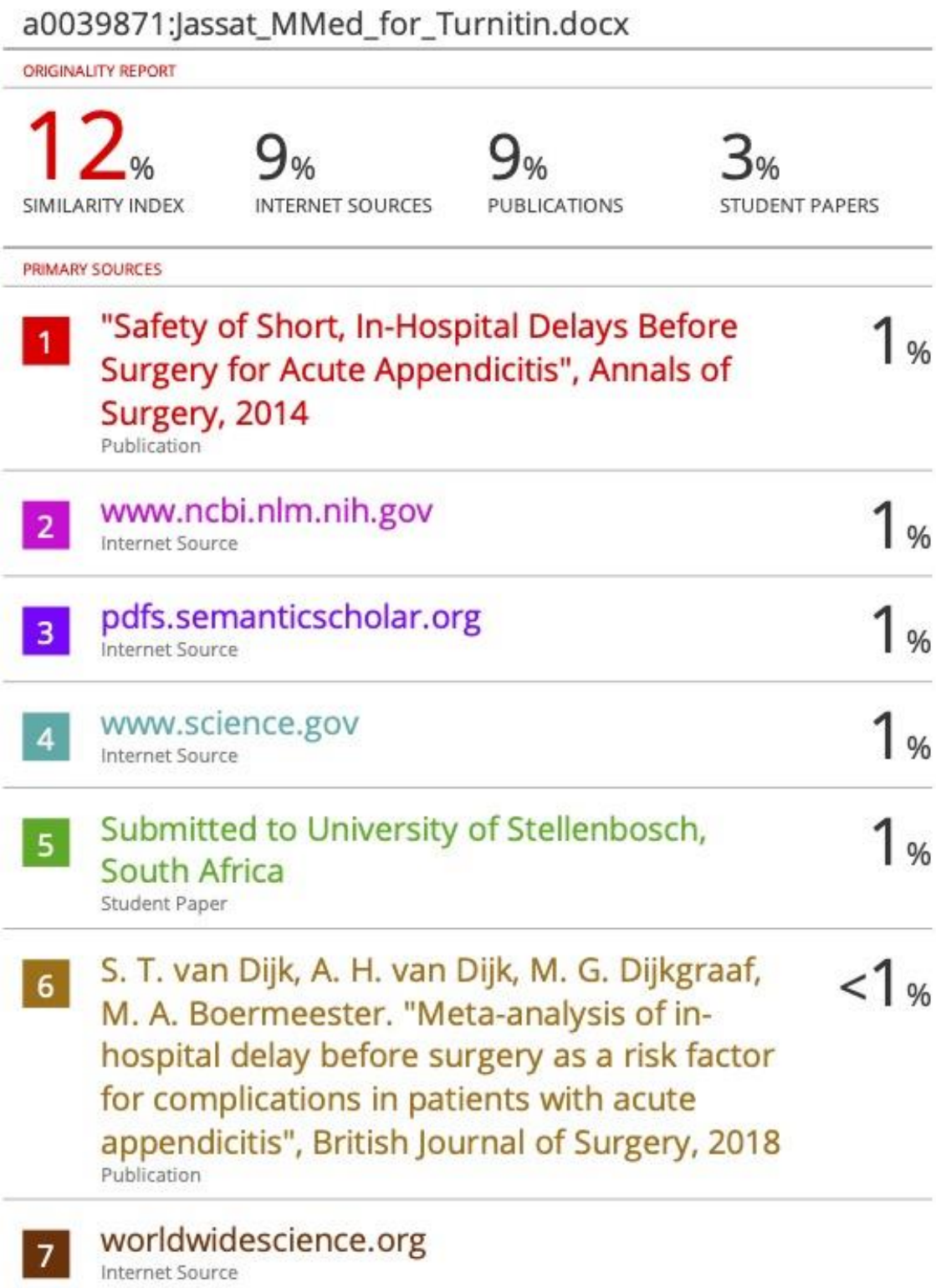
DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized
to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **June** and will therefore be due in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 4: Turn it in plagiarism report



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