A meta-analysis of outcomes of in situ reconstruction after total or partial removal of abdominal infected aortic graft

Short Title: In Situ Reconstruction after Total or Partial Graft Removal.

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ABSTRACT

BACKGROUND. There is currently a lack of evidence for the relative effectiveness of partial resection (PR) and total resection (TR) before managing abdominal aortic graft infection (AGI). Most authorities agree that TR is mandatory for intracavitary AGI in patients with favorable conditions but there is an increasing number of patients with severe comorbidities for whom this approach is not suitable, resulting in a prohibitive mortality rate. The purpose of this study was to determine the most appropriate indication for TR or PR.

METHODS. A meta-analysis was conducted on the rates of early/late mortality, amputations and reinfection. A meta-regression was performed with 8 variables: patient age, male prevalence, presence of virulent or nonvirulent organisms, urgency, omentoplasty and follow-up.

RESULTS. Twenty-one studies and 1.052 patients were included. For TR and PR the rates of early mortality and reinfection were 16.8% and 10.5%, 11% and 27% respectively. For TR urgency and male gender were associated with increased rate of early mortality and male gender, PDF and virulent organisms were associated with increased risk of reinfection. For PR no statistical correlation was analyzable except for PDF with increased risk of reinfection.

CONCLUSION. Early mortality rates are higher for TR and reinfection rates are higher for PR. For TR early mortality increases in urgent cases and it is suggested that alternative option must be discussed, reinfection decreases in the presence of nonvirulent organisms and TR seems optimal. For TR and PR reinfection increases in presence of PDF and alternative technique may be more appropriate.

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Keywords: - meta-analysis- outcomes of in situ reconstruction- infected aortic graft- total or partial removal.

INTRODUCTION

Aortic graft infection (AGI) is a life-threatening complication that occurs in 1% to 5% of patients who undergo conventional abdominal aortic surgery[1-4],causing major morbidity, mortality, and economic cost[5-7] .The prognosis depends on a multitude of factors including the underlying condition of the patient, urgency, presence of sepsis, virulence of the infecting organism(s), infection linked to prosthetic-duodenal fistula (PDF), and finally the surgical modalities of AGI treatment[8-12]. Contemporary management of AGI includes:

- total resection of the infected graft, with either concomitant extra-anatomic reconstruction (EAR) or in situ reconstruction (ISR)[13]

- partial resection (PR)

In a recent meta-analysis, ISR was associated with a lower occurrence of events than EAR, and these results suggest that ISR may be considered as a first-line treatment[14]. Most authorities agree that total resection (TR) of the infected aortic graft is mandatory for intracavitary AGI[15-17]. However, extensive dissection to achieve total graft excision could disrupt the collateral blood supply and create a problem of pelvic and limb ischaemia[18,19]. Moreover, the total graft removal approach is clearly not feasible in some patients with severe comorbidites or extremely hostile abdomens[20].

On the other hand, partial graft preservation techniques are becoming increasingly popular as a method to treat established graft infection[21-25]. However, partial resection (PR) varies widely in the series, there is no consensus for assessing the extent of infection on the graft, indications are not clear, and outcomes reported in the series are limited.

Despite a considerable number of publications including total or partial excision of the infected aortic graft there has been no systematic review or meta-analysis to assess the clinical outcomes of ISR associated with the 2 excision modalities. The

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purpose of this meta-analysis was to determine the most appropriate indication for TR or PR of an infected aortic graft in light of the different outcomes after ISR.

Methods

The present review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [26]. A review protocol can be accessed online in Appendix A.

Research Strategy :

A literature search was performed using MEDLINE and EMBASE, covering all studies published in English between January 1997 and June 2017, as well as recommendations for reporting treatment of aortic graft infections[27]. The medical subject headings (MeSH) used for the search were aortic, graft, and infection. The following key words were also used: Rifampin or Rifampicin-coated polyester grafts, polyester or Dacron, cryopreserved allografts, autogenous veins, Silver-coated polyester, prosthetic-duodenal-fistula, and partial resection (PR), or total resection(TR).

Inclusion and exclusion criteria were defined to determine the selection of clinical studies (detailed online in Appendix B). References from identified studies were also reviewed to ensure that all relevant published papers had been identified. The electronic search was accompanied by a manual search of all the reference lists from the relevant articles.

Study Selection:

The selected clinical studies included ISR with autogenous veins, cryopreserved allografts and synthetic prostheses that were either standard, Rifampicin bonded or Silver coated polyesters. They also included PDF, (classified as a separate entity[27]), and the modality of intervention (emergency or planned) for assessment in the meta-regression analysis. Special attention was paid to the extent of the resection: total resection (TR) or partial resection (PR) of the infected aortic graft.

With no prior knowledge of the authors or the outcomes of the selected publications, two reviewers used a standardized scoring system to rate the clinical

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and methodological quality of each study [28](detailed online in Appendix C). Studies that did not - rate above the 18/28 quality score threshold were excluded from the meta-analysis. All studies that did meet the inclusion and exclusion criteria were found to have a quality score above this threshold. These assigned quality scores were not used to compare the results of individuals studies.

Data Extraction:

When the available written information was insufficient for the meta-analysis, strenuous efforts were made to contact the principal investigator and obtain the necessary information in order to reduce the effect of publication bias.

Two reviewers independently extracted the data from each selected publication. Inter-rater reliability was high. The primary outcome measures were early (< 1 year) and late mortality (> 1 year)[12]. Additional data was extracted regarding rates of amputation and reinfection of the in situ graft".

Statistical Analysis:

The purpose of this meta-analysis was to statistically compare the estimated mean occurrence rate of the following events: early (operative) /late mortality, amputation and reinfection. These rates were pooled from studies including the following variables: age, male prevalence, emergency operation, PDF, omentoplasty, microbiology data and follow-up.

We used Comprehensive Meta-Analysis software to carry out this project. With this software, we estimated the pooled values of the parameters (estimation of frequency in meta-analysis) as well as their confidence intervals.

We estimated the heterogeneity using Cochran's Q test with the point estimate of I^2. Heterogeneity was visually analyzed with a Forestplot, and quantified using Cochran's Q test with the point estimate of I^2. If heterogeneity was present (Q statistic at 5%, and I^2 high), we took it into account using the DerSimonian and Laird random-effects method, and if not, using the fixed-effects method.

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A**s** there were no randomized trials, when we compared 2 groups, we used a percentage comparison test between the 2 independent groups (chi-squared test). We then researched the publication bias using the Egger method and the trim and fill method. With the latter, we reassessed the results and their confidence interval, taking into account potential missing studies belonging to the analyzed pool. Since the percentage tests generally concerned more than 2 modalities, we used the chi-squared test to compare one level with the other levels. When appropriate, correction for multiple comparisons was performed for subgroup analysis.

Meta-régressions were carried out to estimate the heterogeneity effects according to confounding variables, as defined: patient age (above the mean age, patients were defined as older), male prevalence, emergency ISR, presence of PDF, virulent infectious organisms (ie, Staphylococcus aureus, Enterobacteriaceae, beta-hemolytic Streptococcus, Pseudomonas) [29], non-virulent infectious organisms (ie, commensal organisms or negative bacteriological cultures) [29], omentoplasty and follow-up. We performed meta-regressions when the number of studies was higher than or equal to 3. The outcome of these methods enabled us to discuss the final results and justify our propositions.

Besides the meta-analysis software, we used the SAS software version 9.3 at the University Institute of Clinical Research of Montpellier (UPRES 2415 Team. Aide à la décision médicale personnalisée-Personalized support for therapeutic decision).

Results

A total of 2,327 unique articles were identified, 382 of which were retrievied for analysis. Inclusion/exclusion criteria were met by 31 publications. Ten articles were excluded using a standard scoring system. Twenty-one studies and 1,052 patients, were included in this meta-analysis (detailed online in Appendix D). They were classified according to the extent of infection of the aortic graft (either as P0 graft infection of cavitary graft, eg. aorto-aortic or aorto- bi-iliac graft, or as P2 graft infection of extra-cavitary graft, eg. infection of extra-cavitary portion of the graft whose origin is cavitary, eg. aorto-bifemoral graft) [27], and the extent of resection of the infected aortic graft: total resection(TR), or partial resection (PR).

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Nearly all the studies used in this meta-analysis were retrospective and observational. As expected, none of the studies were randomized control trials. The primary characteristics of clinical studies and covariates used in this meta-analysis are detailed online in Appendix E [8-11,24,25,30-44].

The mean number of patients across all studies was 50 (range: 2-220).There were 887 TR (84 %), and 165 PR (16%) with 6 studies (382 patients) combining TR (259 patients) and PR (123 patients) [10,31,34,36,40,42], 11 studies with solely TR (628 patients) [8,9,11,30,32,33,35,37,41,43,44], and 4 studies with solely PR (42 patients) [24,25,38,39].

The mean patient age for the entire series was 66.1 years (range 29-91 years); the mean age of patients with TR and PR was 65.1 years (range 29-86 years), and 67.7 years (range 43-91 years) respectively (P=NS).

Different comorbidities and risk factors, detailed online in Appendix E, were not available in all the studies, and therefore statistical comparison between the outcomes of the patients with TR and PR must be interpreted with caution.

1°Outcomes after total resection:

a) Early mortality:

Separate sets of data were available for 13 studies (642 patients).After correction of bias the adjusted early mortality rate was 16.8%; 95% CI: 11.8%-22.6%, (Table 1A). In a meta-regression analysis (Table 1B) urgency of the intervention (P = .001), male prevalence (P< .0001) and omentoplasty (P< .0001)were associated with increased risk of - early mortality (Figure 1A, 1B, 1C).

b) Late mortality:

Separate sets of data were available for 11 studies (585 patients). After correction of bias, the adjusted late mortality rate was 28.5%; 95% CI: 25%-32%, (Table 1A).In a meta-regression analysis (Table 1B), only omentoplasty (P= .006) was associated with decreased risk of late mortality (Figure 2)**.**

c) Reinfection:

Separate sets of data were available for 16 studies (808 patients) . After correction of bias the adjusted reinfection rate was 11%; 95% CI: 6%-19% (Table 1A).In a meta-

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regression analysis (Table1C), patient age (P< .0001),presence of PDF (P = .002), and virulent infectious organisms (P = .001) - were associated with increased risk of reinfection (Figure 3A, B, C), whereas nonvirulent infectious organisms (P< .0001) was associated with decreased risk of reinfection (Figure 3D).

d) Amputation :

Separate sets of data were available for 14 studies (660 patients) . After correction of bias, the adjusted amputation rate: 8.1%; 95% CI: 6%-11%, (Table 1A).In a meta-regression analysis, (Table1C), presence of PDF (P = .042), and length of follow-up (P = .006), were both associated with increased risk of amputation (Figure 4), whereas male prevalence was associated with decreased risk of amputation (P = .026).

2° Outcomes after partial resection:

a) Early mortality:

Separate sets of data were available for 6 studies (68 patients). After correction of bias, the adjusted operative mortality rate: 10.5%; 95% CI: 4%-22%, (Table 2). In a meta-regression analysis (Table 1B), there was no analyzable correlation between the variables considered (P > .05).

b) Late mortality:

Separate sets of data were available for 5 studies (49 patients). After correction of bias, the adjusted late mortality rate: 18%; 95% CI: 9%-32%, (Table 2).In a meta-regression analysis (Table 1B), there was no analyzable correlation between the variables considered (P > .05).

c) Reinfection:

Separate sets of data were available for 10 studies (165 patients). After correction of bias, the adjusted reinfection rate: 27%; 95% CI: 12%-50%, (Table 2). In a meta-regression analysis (Table 1C), only the presence of PDF (P=.01) was associated with increased risk of reinfection (Figure 5).

d) Amputation:

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Separate sets of data were available for 7 studies (74 patients). After correction of bias the adjusted amputation rate: 15.4%; 95% CI: 8%-29%, (Table 2). In a meta-regression analysis (Table 1C), there was no analyzable correlation with the variables considered (P > .05).

Discussion

Treatment for AGI is still very much under discussion, and optimal management of patients is still an unsolved challenge. Miller [45] was one of the first to introduce the concept of partial aortic graft removal accomplished with a 13% early mortality rate, 33% persistent infection and thereby challenged the paradigm of entire aortic graft excision .

The results from the present meta-analysis are summarized in Table 1A, 2 : early/late mortality, reinfection and amputation rates for TR and PR are 16.8% and 10.5%, 28.5% and 18%, 11% and 27%, and 8.1% and 15.4% respectively . They are in keeping with previously published reviews/ meta-analyses [12-14].However, statistical comparison with TR and PR must be weighted with the limitations of meta-analysis and interpreted with caution (see below).

Perhaps the most difficult aspect of managing AGI is deciding on the appropriate treatment for any given patient :

- regarding the manifestations of the patients concerned, most authorities agree that TR is mandatory for intra-cavitary AGI in patients with favorable conditions[13,15-17], but there is an increasing number of patients with severe comorbidities and for whom this approach would be inappropriate and even ill-advised, resulting in a prohibitive mortality rate. Thus, it was suggested that the premise of a more limited aortic reconstruction might benefit the patient by avoiding aortic clampage, reducing physiological stress, and limiting the extent of dissection needed to excise the entire graft.

- on the other hand, concerning the extent of AGI, numerous authors [38-41, 43-45] agree that for pangraft infection, TR is the most advisable, and when AGI is localized, PR appears recommendable[24,25]. However there are numerous other clinical scenarios

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where optimal treatment is not clearly defined. To make the most appropriate decision, evaluation of outcomes in each situation may be helpful.

Early and late mortality:

In the meta-analysis, operative mortality rates were higher for TR than PR, with 16.8% and 10.5% respectively (Table 1A, 2).

In the literature review, urgency of the intervention for AGI is one of the most important determinants of in-hospital mortality [9,12,18,40,46-52]. Not surprisingly, in the meta-regression analysis (Table 1B), urgency had a negative correlation with operative mortality for TR (Figure 1A), but no correlation was analyzable for PR. Hence, in order to lower operative mortality in an emergency situation, there may be fewer surgical options available for patients who cannot be stabilized long enough to select the most appropriate surgical option. In this difficult situation, it is suggested that endovascular bridge therapy might be the only realistic option [13,-53-56].

Male gender was prevalent in this study (online Appendix E). In the meta-regression (Table 1B), male gender had a negative correlation with operative mortality for TR (Figure 1B), but no correlation was analyzable for PR. In the literature female gender was considered as an independent predictor for operative mortality [18]. In the results of the present study, the higher operative mortality observed in males is probably related to the epidemiology of cardiovascular disease and the prevalence of cardiovascular risks in males [57].

In 1987,Walker was one of the first to propose omentoplasty for protection against reinfection [58], and its benefits were confirmed by numerous studies for both TR and PR [9,11,13,18, 37,54] In the meta-regression(Table 1B), the negative correlation between omentoplasty and operative mortality is not clear (Figure 1C), because omentoplasty is considered a safe procedure, associated with a moderate number of post-operative complications [59]. In our opinion, such discrepancy could only be explained by the differences amongst patients undergoing surgical procedures, particulary any underlying diseases.

In the meta-analysis, late mortality rates were higher for TR than for PR with 28.5% and 18% respectively (Table 1A, 2), and in the meta-regression, omentoplasty had a

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positive correlation with late mortality for TR (Figure 2), although no correlation was analyzable for PR (Table 1B). Such benefits for patients with omentoplasty are probably linked to the decrease in late infectious mortality caused by dehiscence of anastomosis and fatal hemorrhage.

Reinfection and amputation:

In the results of the meta-analysis reinfection rates were higher for PR than for TR, with 27% and 11% respectively (Table 1A, 2). The literature [60-62] supports this idea that complete graft excision minimizes the risk of reinfection and Ricotta reported persistent or recurrent infection in 25% of the grafts treated with PR but no reinfection after TR [62].

In the literature there is a link between reinfection and patient age [10,11,63], presence of PDF[10,12,18,47,48,64] and virulent[10,25,32,43,48,65-67] or nonvirulent[64,68-70]-infecting organisms. In the meta-regression (Table 1C), age and virulent organisms had a negative correlation with reinfection for TR (Figure 3A, C), nonvirulent organisms had a positive correlation for TR (Figure 3D), and PDF had a negative correlation for TR and PR (Figure 3B, Figure 5). The results of the present study suggest that in order to lower reinfection rates in the presence of nonvirulent organisms, TR appears optimal. In the presence of PDF, neither TR nor PR were advisable before in situ reconstruction. It was suggested that extra-anatomic bypass still has an important role [18,71], and staged endovascular approach with early conversion to in situ repair with a vein or prosthetic graft with omental wrapping may achieve the best results[55] . For older patients or in the presence of virulent organisms fewer surgical options may have been available because TR was not recommendable and PR had no analyzable correlation. Thus, for older patients or in the presence of virulent organisms, if the patient is hemodynamically stable and not septic, it has been suggested that percutaneous drainage of peri-aortic abcesses or fluid collections, and intensive treatment of infection or comorbidities could be done before more extensive operation [72], and consequently, extra-anatomic reconstruction [18] or in situ reconstruction with femoral veins [12,14] may be the most appropriate .

Omentoplasty was recommended to lower reinfection rates[9,11,13,18,24,31,37,58]. Unfortunately, in the present study, no correlation was analyzable. However,

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omentoplasty is not always feasible, for instance in the event of extra-cavitary graft infection or a retroperitoneal approach [24,25].

In the results of the meta-analysis, amputation rates were higher for PR than for TR, with 15.4% and 8.1% respectively (Table 1A, 2). Unsurprisingly, in the meta-regression (Table 1C), amongst the population of patients with vascular risks, follow-up had a negative correlation with amputation for TR (Figure 4), and the results for PR were not analyzable. The nature of the conduit was probably the major factor [12,14] .

This meta-analysis suggests indications for PR or TR of infected aortic graft according to patient manifestations and the bacteriologic data, but unfortunately it could not provide any recommendations as to how to make future decisions regarding patient treatment because this study is a meta-analysis of retrospective studies, not prospective, nor randomized. Moreover, observational studies used in this meta-analysis were difficult to analyze and interpret because the discrepancy between patient numbers in each group (887 TR vs 165 PR) caused a problem for statistical comparison. This drawback was owing to the lack of standardized indications for TR or PR in the series, and not this meta-analysis.

Finally, the main finding of this study was the reduced post-operative mortality with PR at the price of the increased late reinfection. Therefore, management of AGI is clearly not easy, and is still under discussion. In order to define an optimal strategy, decisions must be tailored following the input of all clinicians involved, i.e. vascular surgeon, microbiologist/infectious disease physician, interventional and imagist radiologist and others, taking due cognizance of the individual patient's condition and state [13, 73-77]. Moreover, operative flexibility is required should unexpected difficulties arise during the intervention.

Study Limitations:

Some limitations, mostly related to potential bias, are encountered in this meta-analysis:

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- Studies selection bias:

The selection process for publications, notably the manner in which we pooled the data from individual studies, may be a source of bias. Inclusion/exclusion criteria were defined in attempt to limit selection bias. For example, infected aortic aneurysms were excluded because, etiology, bacteriology and treatment results are different from those of AGI [13,48,78], and the series combining total and partial removal of infected aortic grafts were excluded if the results were not differentiated. On the other hand, our inclusion/exclusion criteria may have biased the outcome of the meta-analysis. For example, we only considered clinical studies whose results were reported in the English language. Hence, results extracted from medical journals in languages other than English were excluded. We believe that publication bias was limited by the use of the Funnel plots and complementarity validation tests.

- Outcome reporting bias:

Nearly all studies analyzed were retrospective and observational. Consequently, there are problems concerning inter-study heterogeneity and selection bias [79] despite reasonable efforts to perform tests of heterogeneity (Table 1A, 2):

- it is possible that some significant medical considerations were not available in a number of studies. These include, cigarette smoking (not reported in the majority of the series) which is associated with increased surgical risk of site infection[80],time to clinical presentation of the infection divided into early and late presentation (<3months or after 3 months)[23], infection presented, and specific informations on the pre-operative status of the patients: coronary heart disease, HTA, diabetes mellitus, renal failure, chronic obstructive pulmonary disease, ASA score, immunosuppression, history of neoplasm, body mass index[81], anatomic considerations (hostile abdomens, poor pelvic collateral blood supply, tight attachment of the infected graft to the iliac vessels and the ureter, aortic graft involving the renal or visceral aortic segment), and so forth. These risk of bias across the studies create reservations regarding the comparison of outcomes after TR and PR[27]. For example, partial graft removal of the infected aortic graft was probably performed in a group of patients who have a more significant operative risk compared to those who underwent total graft removal, but these differences,

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despite reasonable efforts, cannot be shown in the different studies. This drawback concerns the reported studies themselves and not this meta-analysis.

- there is also a possibility that some specific aspects of treatment were not available, yet had an impact on perioperative outcomes: drainage of peri-prosthetic abscesses, use of sartorius flap[21] or Vacuum- assisted closure device, the experience of each center (number of patients treated per year for AGI), lack of consensus concerning the nature and duration of postoperative antibiotherapy[82], and so forth.

As a result, the eligible sample size for analysis was considerably reduced. However, this drawback concerns the reported studies themselves and not this meta-analysis.

- Limits of meta-regression:

The associations derived from meta-regression are observational and have a weaker interpretation than the causal relationships derived from randomized comparisons. Data dredging is the main pitfall in reaching reliable conclusions from meta-regression, and pre-specification of covariates is heightened. Therefore, special attention was paid to selected relevant covariates in this study. For instance, the nature of the conduit has an impact on operative outcomes [12,14], but these differences could not be captured in the present meta-analysis owing to heterogeneity between PR and TR.

Conclusion

The results of this meta-analysis suggest that operative mortality rates are higher for TR , and reinfection rates are higher for PR .

Operative mortality increases in urgent cases for TR . Hence in order to lower operative mortality in an emergency situation it is suggested that alternative option must be discussed.

Reinfection decreases for TR in the presence of nonvirulent infectious organisms, and in order to lower reinfection TR seems optimal. In the presence of virulent

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organisms and PDF reinfection increases for TR and alternative techniques may be most appropriate.

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Legends of Tables and Figures

Table I: Meta-Analysis and Heterogeneity Tests of the Results for Total Resection.

Table II: Meta-Regression Analysis of the Risk of Operative and Late Mortality According to Male gender, Omentoplasty and Emergency.

TR: total resection; PR: partial resection.

Table III: Meta-Regression Analysis of the Risk of Reinfection and Amputation According to Age, PDF,Virulent or Nonvirulent Infecting Organisms, Follow-up and Male gender.

TR: Total Resection; PR: Partial Resection, PDF: prosthetic-duodenal fistula, % male : male gender.

Table IV: Meta-Analysis and Heterogeneity Tests of the Results for Partial Resection.

Figure 1A: Meta-regression plot of emergency against early mortality for total resection (10 studies, P = .001, Tau^2 = .10).

Figure 1B: Meta-regression plot of presence of male gendre against early mortality for total resection (10 studies, P = 0, Tau^2 = .144).

Figure 1C: Meta-regression plot of omentoplasty against early mortality for total resection (3studies, P = 0, Tau^2 = .054).

Figure 2: Meta-regression plot of omentoplasty against late mortality for total resection (3 studies, P = .006, Tau^2 = 0).

Figure 3A: Meta-regression plot of age against reinfection for total resection (11 studies, P = 0, Tau^2 = .75).

Figure 3B: Meta-regression plot of presence of prosthetic-duodenal fistula against reinfection for total resection (11 studies, P=.002, Tau^2 = .85)

Figure 3C: Meta-regression plot of virulent infectious organisms against reinfection for total resection (11studies, P = .001, Tau^2 = 1.24).

Figure 3D: Meta-regression plot of nonvirulent infectious organisms against reinfection for total resection (10 studies, P = 0, Tau^2 = .33).

Figure 3D: Meta-regression plot of presence of prosthetic-duodenal fistula against reinfection for total resection (11 studies, P=.002, Tau^2 = .85)

Figure 4: Meta-regression plot of follow-up against amputation for total resection (11 studies, P = .006, Tau^2 = .15).

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Figure 5: Meta-regression plot of prosthetic-duodenal fistula against reinfection for partial resection (4 studies, P = .01, Tau^2 = 0).

	No of trials analysis	I^2 statistic	P for heterogeneity	Method (fixed or Random-effects Model)	Event Rate	IC Event Rate
Random model if heterogeneity test is significant or fixed model if not	13	61.3	0.002	Random	0.162	0.113-0.226
- Operative mortality						
- Reinfection	16	69.7	0	Random	0.064	0.034-0.117
- Amputation	14	29.7	0.14	Fixed	0.068	0.048-0.095
- Late mortality	11	37.4	0.1	Fixed	0.279	0.243-0.319
Event rates after corrections of selection bias (Dural and test is trim and fill)						
- Operative mortality					0.168	0.118-0.226
- Reinfection					0.110	0.06-0.19
- Amputation					0.081	0.06-0.11
- Late mortality					0.285	0.250-0.320

Table - I

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Event	Variables	group	Study N	Slope	Slope 95 % IC	p-value	T^2
	% male	TR	10	0.04	-0.02-0.06	0	0.144
		PR	3	0.06	-0.05-0.17	0.27	0
	Omentoplasty	TR	3	0.05	0.02-0.08	0	0.054
		PR	No correlation analyzable				
Operative Mortality	Emergency	TR	10	0.04	0.02-0.06	0.001	0.10
		PR	No correlation analyzable				
Late Mortality	Omentoplasty	TR	3	-0.09	-0.16-(-0.03)	0.006	0
		PR	No correlation analyzable				

Table II

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Event	Variables	group	Study N	Slope	Slope 95 % IC	p-value	T^2
Reinfection	Age	TR	11	0.29	0.12-0.46	0	0.75
		PR	4	0.16	-0.03-0.35	0.095	1.76
	PDF	TR	11	0.04	-0.01-0.06	0.002	0.85
		PR	4	0.07	0.01-0.13	0.01	0
	Virulent	TR	11	0.06	0.02-0.10	0.001	1.24
		PR	5	-0.00009	-0.18-0.18	0.99	0
	Non Virulent	TR	10	-0.09	-0.13-(-0.05)	0	0.33
		PR	3	-0.02	-0.82-0.77	0.95	0
Amputation	PDF	TR	11	0.02	0.00-0.05	0.042	0.28
		PR	3	0.02	-0.07-0.11	0.66	0.09
	Follow-up	TR	11	0.04	0.01-0.06	0.006	0.15
		PR	4	-0.02	-0.11-0.06	0.57	0
	% male	TR	11	-0.04	0.08-(-0.005)	0.026	0.32
		PR	3	0.05	-0.06-0.16	0.34	0

Table III

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	No of trials analysis	I^2 statistic	P for heterogeneity	Method (fixed or Random-effects Model)	Event Rate	IC Event Rate
Random model if heterogeneity test is significant or fixed model if not	6	0	0.8	Fixed	0.073	0.027-0.18
- Operative mortality						
- Reinfection	10	69.1	0.001	Random	0.189	0.081-0.383
- Amputation	7	0	0.67	Fixed	0.095	0.041-0.206
- Late mortality	5	0	0.64	Fixed	0.162	0.079-0.305
Event rates after corrections of selection bias (Dural and test is trim and fill)					0.105	0.04-0.22
- Operative mortality						
- Reinfection					0.27	0.12-0.50
- Amputation					0.154	0.08-0.29
- Late mortality					0.18	0.09-0.32

Table IV

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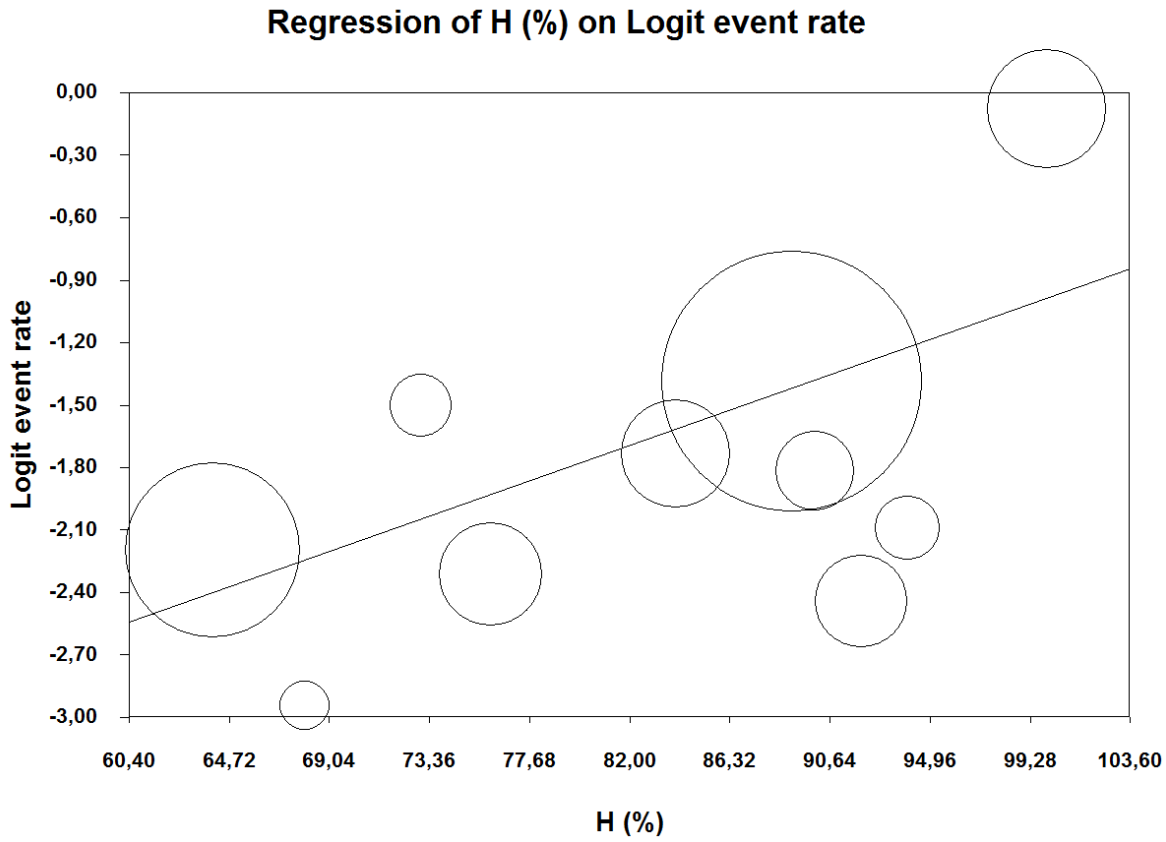
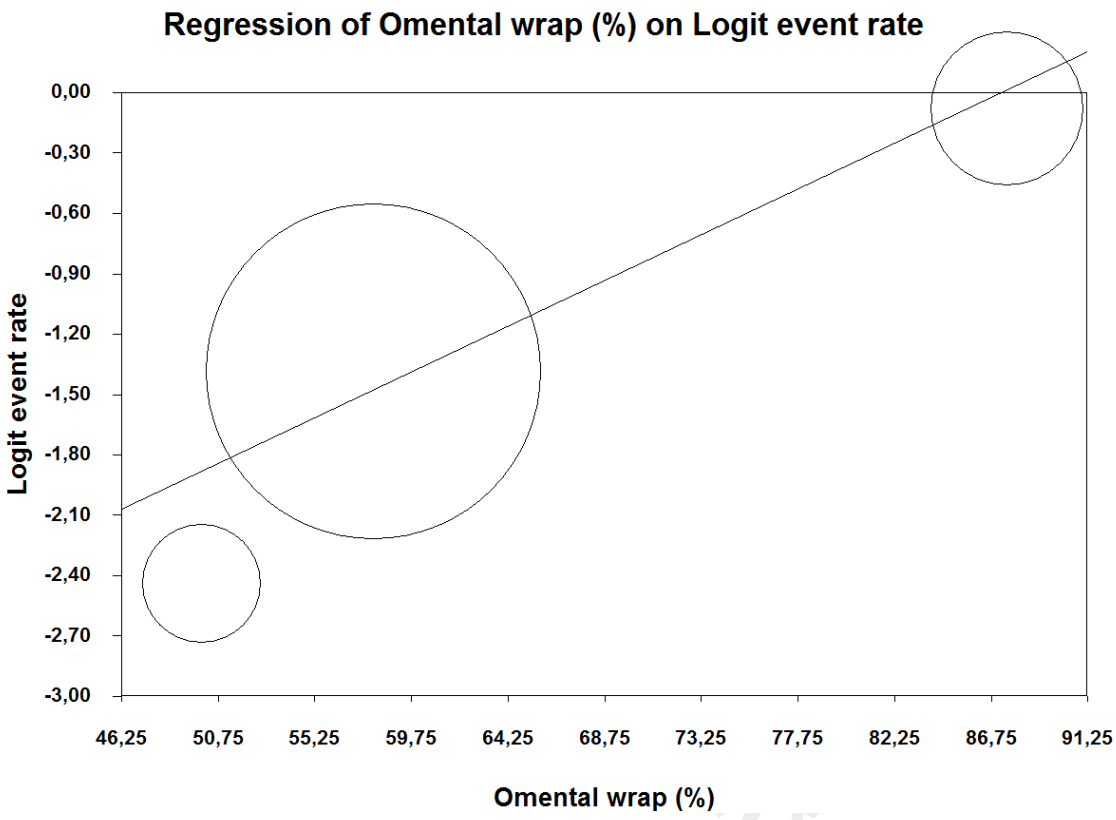


Fig. 1B

Figure 1B

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Fig. 1C

Figure 1C

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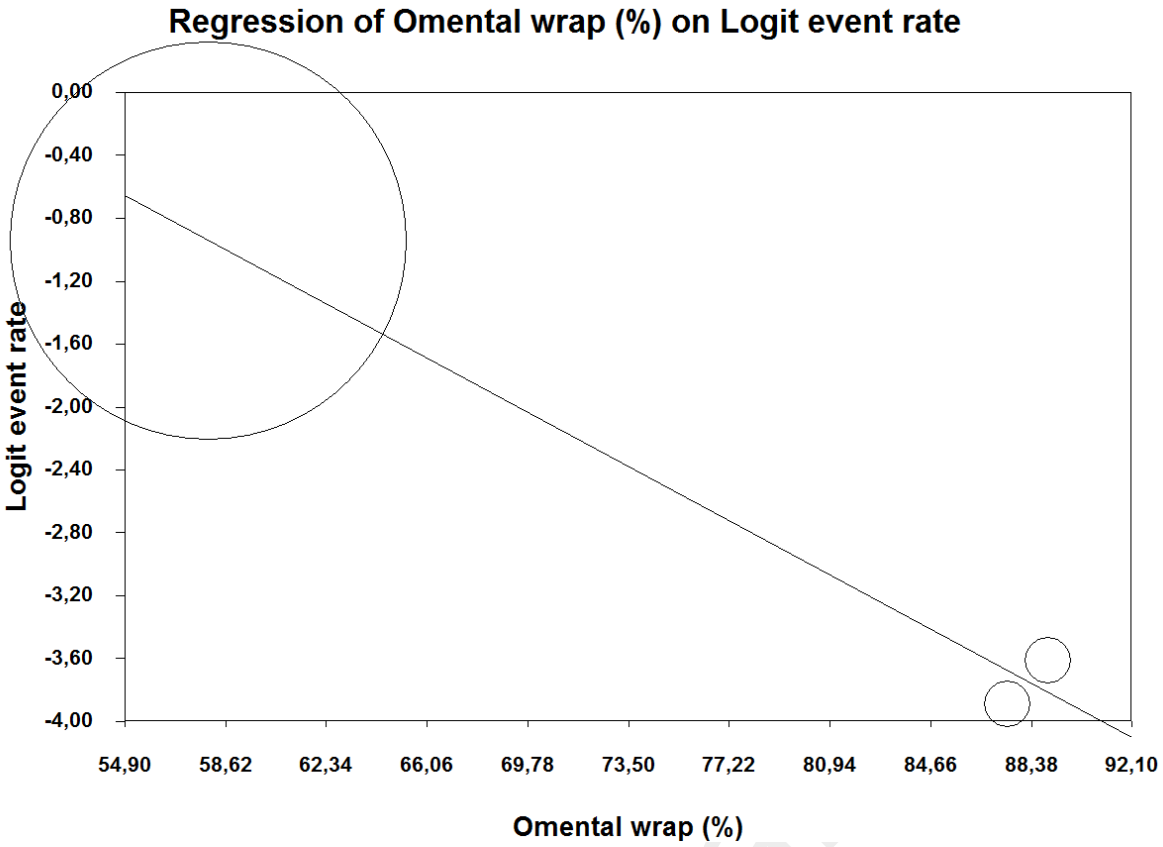


Fig. 1D

Figure 2

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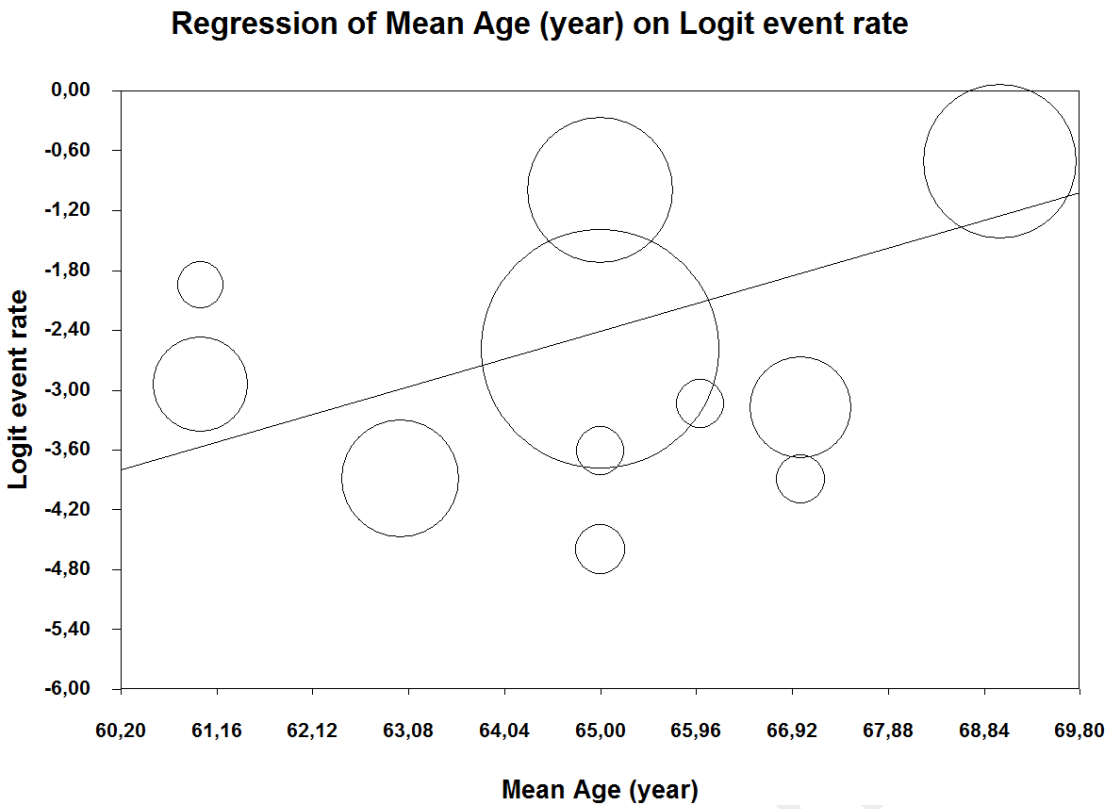


Fig. 2A

Figure 3A

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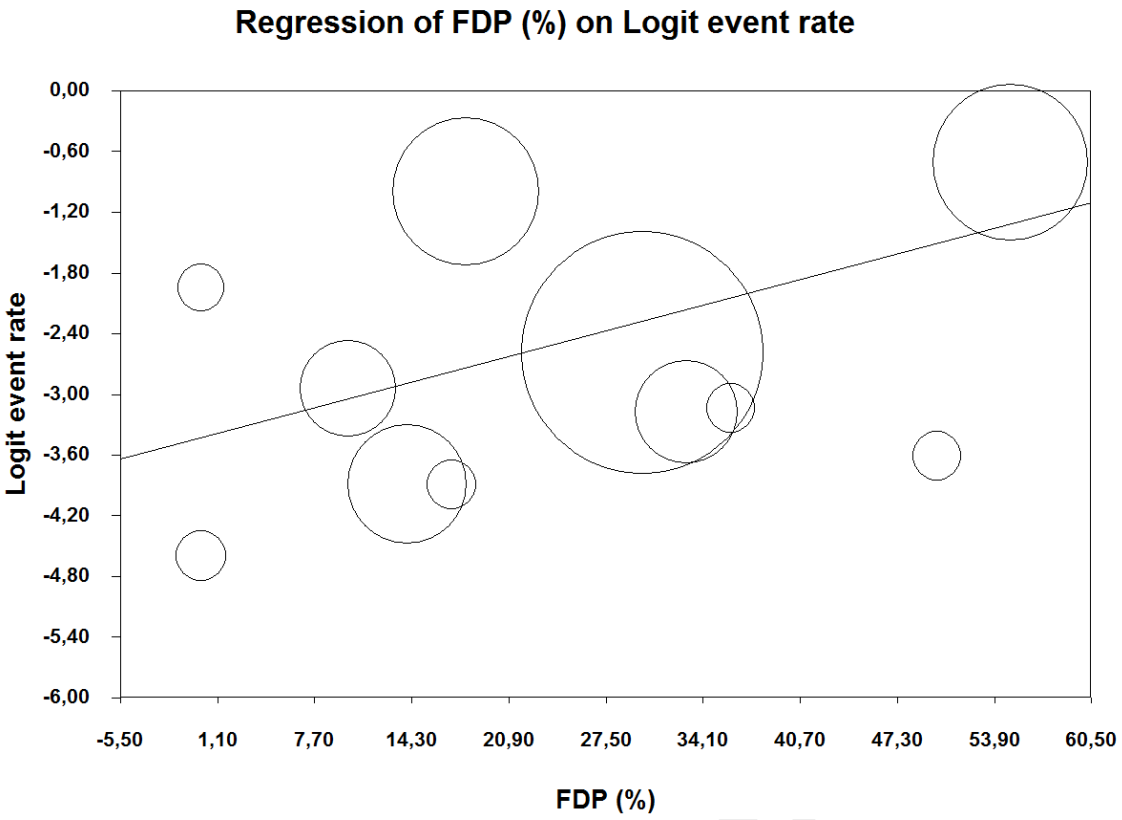


Fig. 2B

Figure 3B

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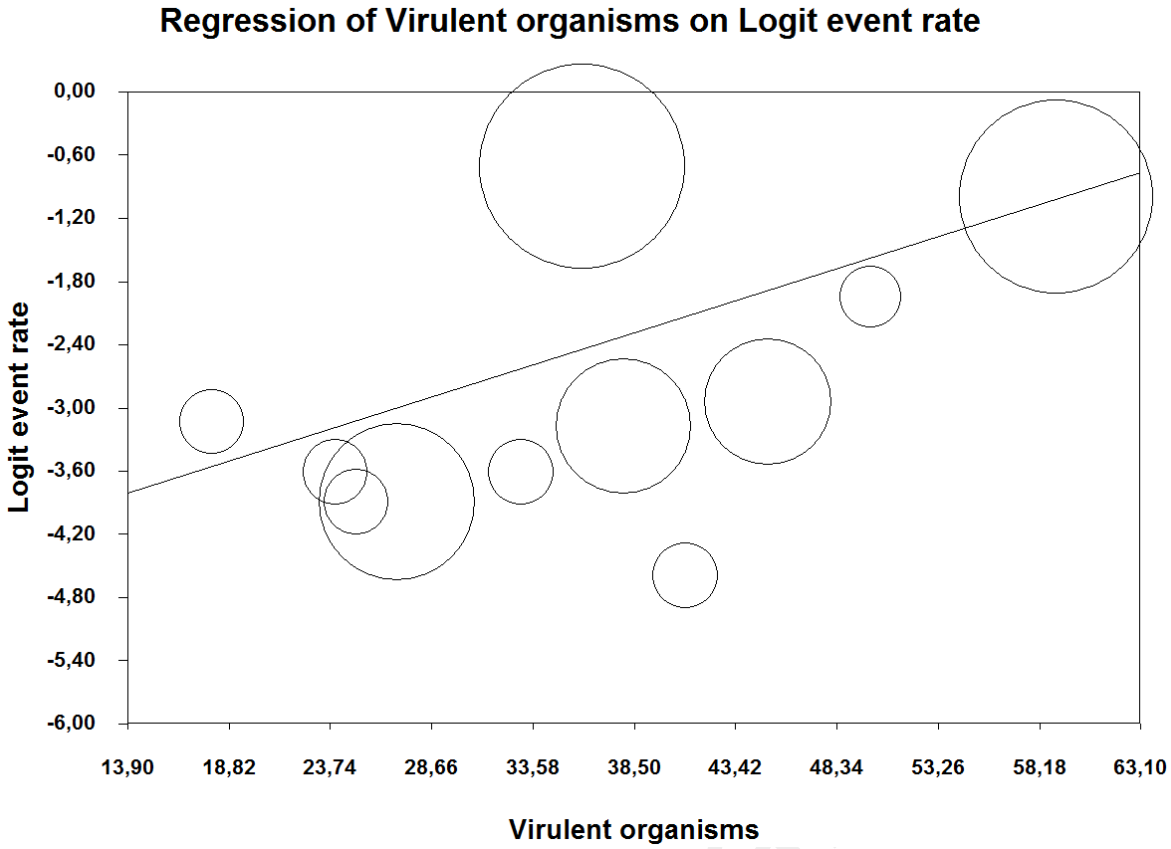


Fig. 2C

Figure 3C

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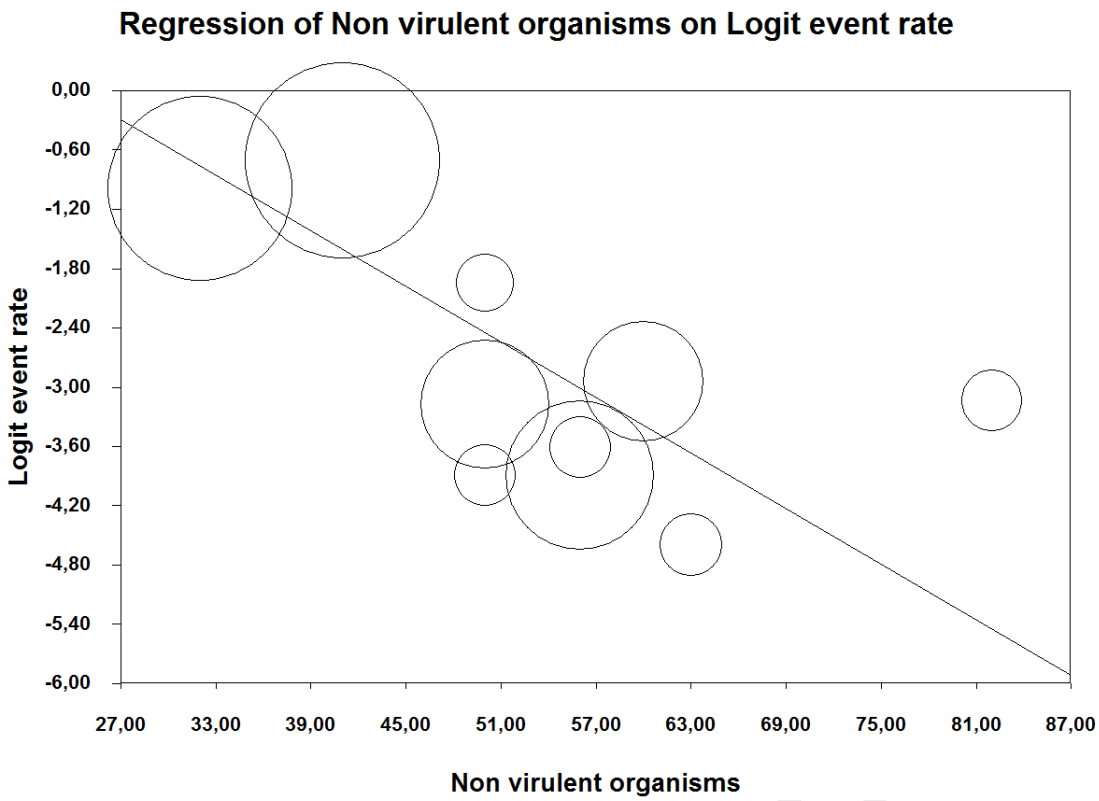


Fig. 2D

Figure 3D

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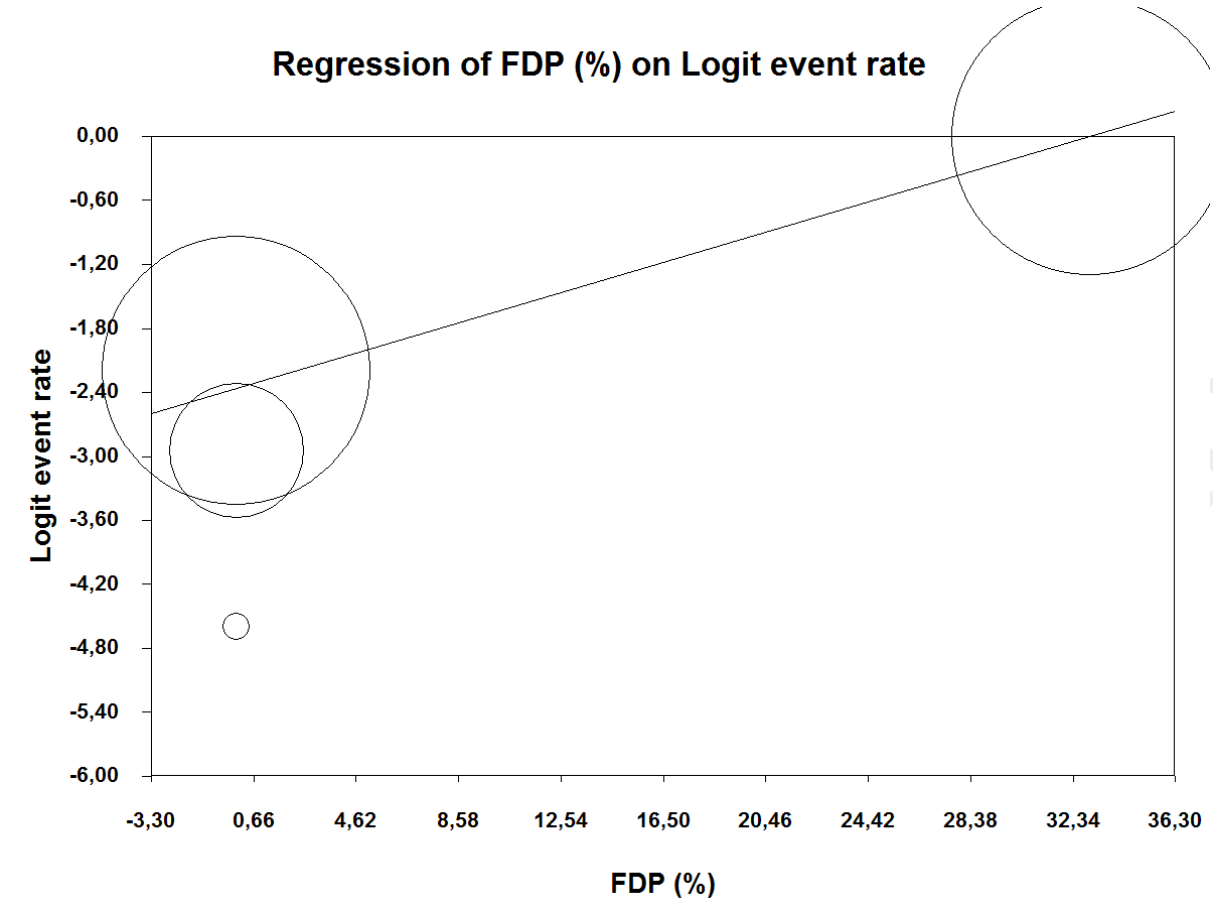


Fig. 2E

Figure 5

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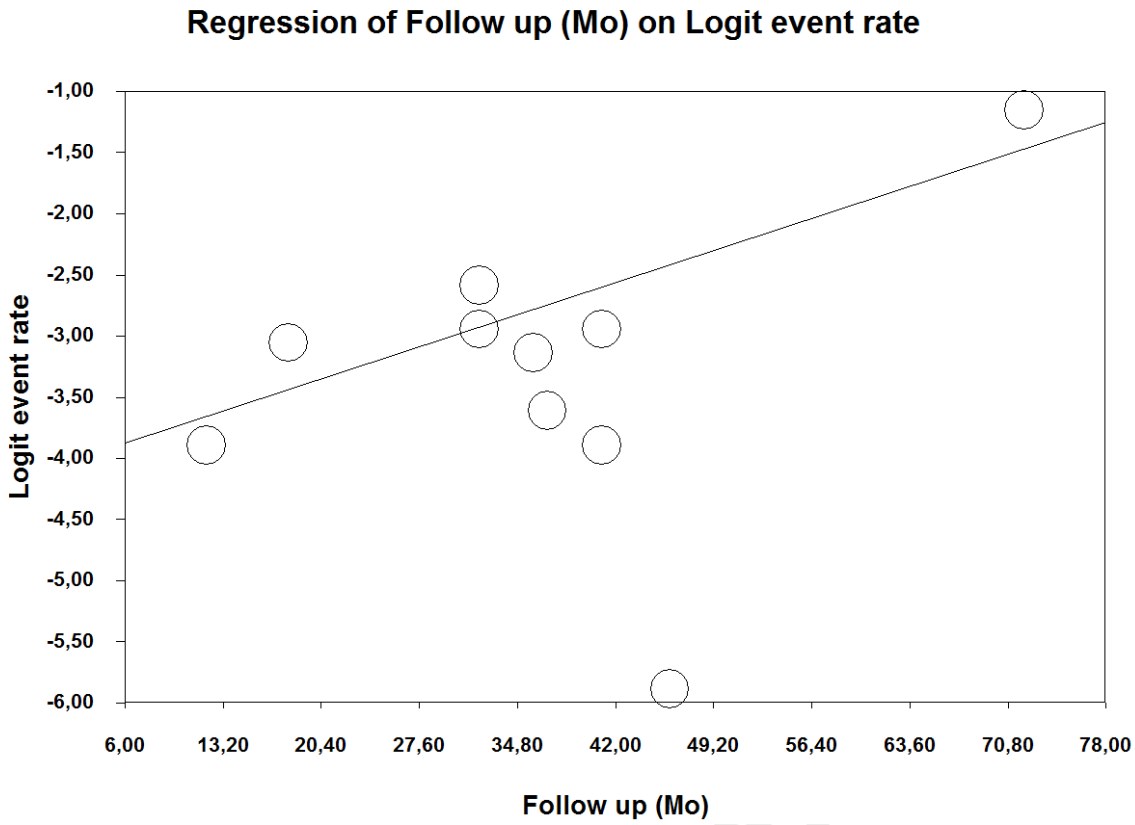


Fig. 3

Figure 4

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