Antibiotics for Fever After Gastric Endoscopic Submucosal Dissection May Be Unnecessary: A Propensity Score-Matching Analysis

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Research article

Keywords: Endoscopic submucosal dissection, Gastric lesions, Antibiotics, Fever, Propensity score-matching analysis

Posted Date: September 28th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-74179/v1

Version of Record: A version of this preprint was published on February 12th, 2021. See the published version at https://doi.org/10.1186/s12876-021-01602-1.

Abstract

Background: Endoscopic submucosal dissection (ESD) has been widely used and has gradually become the main endoscopic treatment for gastrointestinal mucosal and submucosal lesions. Whether antibiotics are necessary for fever after gastric ESD remains unclear. The aim of this study was to analyse the value of the use of antibiotics for fever after ESD.

Methods: In this retrospective study, patients with fever after ESD from January 2014 to January 2019 were included and divided into 2 groups: the antibiotic group and the non-antibiotic group. Fever and hospitalization time were compared between the 2 groups after propensity score (PS) matching.

Results: A total of 451 patients with fever after ESD were included in the present study. with 240 patients in the non-antibiotics group and 211 patients in antibiotics group before matching and 96 patients in the non-antibiotics group and 96 patients in antibiotics group after matching with all baseline characteristics balanced ($p > 0.05$). Fever duration was not significantly different between the 2 groups ($p=0.074$). However, the median hospital stay in the antibiotic group was longer than that in the non-antibiotic group (8 vs 7, $p=0.006$).

Conclusions: Antibiotics for fever after gastric ESD may be unnecessary.

Introduction

Endoscopic submucosal dissection (ESD) has been commonly used as a minimally invasive treatment for gastric lesions[1–3]. Compared with conventional surgical treatment, ESD is associate with shorter operative times, shorter hospital stays and lower complication rates[4, 5], and long-term survival appears equivalent between ESD and gastrectomy patients[6]. However, ESD is associated with some complications, such as perforation, bleeding, and pyrexia. Among the complications, pyrexia is a common complication after ESD, and previous study have reported that fever occurs in 19.5% of cases[7]. Bacteraemia, exposure of large wounds and long operation times may be correlated with pyrexia in patients treated after ESD[7–9]. However, the exact mechanism still needs to be investigated further.

At present, it is almost a consensus that there is no indication for prophylactic antibiotics in gastric ESD. Since, many studies have shown that although continuous submucosal defects caused by ESD may increase the risk of bacteraemia and/or endotoxaemia, the rate of bacteraemia after ESD remains low or the bacteraemia is transient. Therefore, the researchers concluded that prophylactic antibiotics might not be necessary for patients after ESD[8–12]. However, these studies only focused on whether antibiotics were used in advance after ESD. It remains uncertain whether antibiotics are necessary for fever after gastric ESD since post-ESD bacteraemia is transient and the use of antibiotics will increase the cost of hospitalization. Relevant research is rare. Hence, the purpose of this study was to analyse the need for antibiotics for fever after ESD.

Methods

Participants

This is a retrospective study performed at the Department of Gastroenterology, the First Affiliated Hospital of Nanchang University in China. Patients who underwent ESD for gastric lesions at our department between January 2014 and January 2019 were enrolled. Informed consent was obtained from every patient. The exclusion criteria were as follows: (1) did not have a body temperature exceeding 37.5 °C after ESD (regardless of the duration of the fever period); (2) age younger than 18 years or older than 85 years; (3) the use of antibiotics within 2 weeks before ESD; (4) immunodeficiency status; (5) serious cardiovascular, cerebrovascular, or hepatorenal diseases; (6) fever (temperature≥37.5 ℃) before the procedure; (7) patients with incomplete demographic data. This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University.

Relevant definitions

Intraoperative bleeding refers to any bleeding in which haemoglobin is diluted from preoperative level to a level > 2G/dl the day after ESD. Perforation is defined as other organs, extraluminal fat, or extraluminal space outside the muscle layer that can be seen through endoscopy during the ESD operation, regardless of air accumulation in the abdominal cavity, retroperitoneum or

mediastinum[13]. En bloc resection is defined as the endoscopic removal of a lesion in one piece and the acquisition of a single specimen. ESD operation time is defined as the period from intraoperative marking time to withdrawal time. Fever is defined as a temperature >37.5 °C after the ESD procedure (regardless of the duration of the fever period). Because the fever time could not be accurately recorded in minutes, we recorded fever duration < 1 day, >1 day ≤ 2 days, >2 days ≤ 3 days, >3 days ≤ 4 days, and >4 days ≤ 5 days as 1, 2, 3, 4, and 5 days, respectively.

Gastric ESD procedure

Before the ESD procedure, patients underwent an endoscopic ultrasound (EUS) test with a radial-scanning echo endoscopy unit (UM240; Olympus Co., Ltd., Tokyo, Japan) or a 12-Fr catheter probe (UM-3R, 12 MHz; Olympus Co., Ltd., Tokyo, Japan) to identify the size, shape and layer of origin of the tumour. In addition, abdominal computerized tomography (CT) was performed to evaluate the tumour location, growth pattern (intra/extraluminal) and the possibility of lateral growth or distant metastasis. All ESD procedures were performed by experienced endoscopists with more than 10 years of experience. A single-channel endoscope (GIF-Q260J; Olympus Co. Ltd, Tokyo, Japan) was used in this procedure. After intravenous anaesthesia with propofol, routine vital sign monitoring was performed. After identifying the gastric lesions through endoscopy, dots were marked around them with argon plasma coagulation (APC, 40 W soft coagulation). Then, 250 ml glycerol fructose, 2—3 ml indigo carmine and 1 ml 1:10,000 epinephrine were injected into the submucosal layer to elevate the lesion. The superficial mucosa was incised along the outer edge of the marker point by endoscopists using a hook knife (KD 620LR, Olympus). Subsequently, an IT knife-2 (KD 611L, Olympus) was used to gradually separate the submucosal layer and lesion, and a snare (SD-230U-20; Olympus) was used to help with the removal of the lesion if necessary. If the gastric lesions originating from submucosal layer or superficial muscularis propria (MP) layer endoscopic submucosal excavation (ESE) was used. ESE is the derivative technology of ESD. On the basis of ESD technology, continue to gradually peel off the submucosa and part of the muscularis propria at the base of the tumor. If the tumor was located in deep MP layer with extraluminal growth pattern or closely adhered to serosal layer, endoscopic full-thickness resection (EFTR) was chosen for safe and complete tumor removal. The difference between EFTR and ESE was the need for active perforation. In order to achieve complete resection, the tumor, the adjacent MP and serosa were removed. Hot biopsy forceps (FD-410LR; Olympus) or argon plasma coagulation (APC 300, ERBE) were used for intraoperative haemostasis. If there was active perforation caused by tumour excavation, titanium clips (HX-610-135; Aomori Olympus) or an over-the-scope clip system (OTSCs, Ovesco Endoscopy AG, Tübingen, Germany) were used to close the perforation. After removing the lesions, a stomach tube was placed based on the experience of endoscopists to reduce gastric pressure for at least 24 h. All specimens were measured and immersed in formalin and were sent to the pathology department for immediate identification of the nature of the lesion.

Postoperative management

Patients were sent to our ward after recovery from anaesthesia and were asked to fast for 2-5 days. All of the patients received infusions (electrolytes, etc.), gastric mucosal protective agents and proton pump inhibitors (PPIs). The stomach tube was removed according to each patient's condition. If patients had a fever after ESD, they were treated according to the experience of the doctors (either physical cooling, observation treatment, or use of second-generation antibiotics for three consecutive days depending on the situation), and their temperature was recorded once a day until their temperature returned to normal. If they did not have any complications after ESD, they were permitted to return to a normal diet gradually.

Statistical analysis

We divided the patients into two groups according to whether antibiotics were used. The variables are presented as the mean ± standard deviation (SD), the median and interquartile range (IQR) or proportion, as appropriate. Propensity score (PS) analysis was performed as a nonrandomized sensitivity analysis to control and reduce the selection bias of each group. PS was estimated by using a multivariable logistic regression model with the following covariates: age, sex, diabetes, hypertension, previous abdominal surgery, lesion location, tumour size, pathology, intraoperative bleeding, perforation, operation time, en bloc resection, maximum body temperature, and stomach tube. The match ratio was 1:1, and the "nearest neighbour matching" method was used (calliper width=0.02). The absolute standardized difference (ASD) was used to assess the balance of covariates between the

two groups. An ASD 0.1 signifies a good balance for a particular covariate. Then, we compared the fever days and hospitalization days between the two groups after matching.

The differences in baseline characteristics between the antibiotic and non-antibiotic groups were assessed using Student's t-test for continuous variables of a normal distribution, the chi-square test or Fisher's exact test for categorical variables, and the Wilcoxon rank-sum test for rank variables and continuous variables of a abnormally distributed, as appropriate. $P<0.05$ was considered to be statistically significant. Statistical analyses were performed using R statistical software 3.6.1 (www.r-project.org) and IBM SPSS Statistics for Windows (V. 23.0).

Results

Cohort characteristics

A total of 1955 patients who had gastric lesions underwent ESD during the study period at our centre. Of these, 451 patients (23.07%, Fig. 1) with fever after the procedure were included in this study. Table 1 shows the baseline characteristics of the cohort. The median age (IQR) of these patients was 54 (46-62) years, and 302 (67%) patients were female. A total of 211 patients received antibiotics when they had pyrexia after ESD, while 240 did not receive antibiotics. Before PS matching, there were significant differences in 6 factors between the 2 groups, as follows: age ($p = 0.047$), lesion location ($p<0.001$), perforation ($p<0.001$), operation time ($p<0.001$), maximum body temperature ($p<0.001$) and stomach tube ($p = 0.019$). After PS matching, a total of 192 patients were paired for the analysis. There was no significant difference in the baseline characteristics between the pairs, and the scatter diagram (Fig. 2) and histogram (Fig. 3) of the tendency distribution show good matching. The ASD for all matched covariates was < 0.1.

Comparison between the non-antibiotic group and the antibiotic group

After PS matching, the selection bias of each group was reduced and controlled. The fever durations between the two groups were compared by rank sum test, and the hospitalization time between the two groups was compared by Student's t-test. The rank average of fever duration in the antibiotic group was higher than that in the non-antibiotic group, but the results were not significant (102.55 vs 90.45, $p=0.074$). However, the median length of hospital stay in the antibiotic group was longer than that in the non-antibiotic group (8 vs 7, $p=0.006$)(Table 2).

In the subgroup analysis, when maximum body temperature was <38.5 °C, the median hospitalization duration of the antibiotic group was still longer than that of the non-antibiotic group (8 vs 7, $p=0.009$), and the comparison of fever duration was still nonsignificant (94.32 vs 82.55, $p=0.061$)(Table 3). In the subgroup with a temperature ≥ 38.5 °C, the comparison between the two groups in average hospitalization duration in days (9.71 ± 1.56 vs 7.67 ± 2.29, $p=0.455$) and the rank mean of fever duration in days (7.39 vs 9.93, $p=0.299$) were not significant.

Discussion

Fever is one of the common complications after ESD, but the mechanism of fever development after ESD is still unclear. Previous studies have indicated that fever after ESD may be related to wound exposure and bacteraemia[10]. Some guidelines have recommended prophylactic use of antibiotics after ESD[14, 15]. However, Kato et al. found that the incidence of bacteraemia after ESD was low[11]. Lee et al. found that bacteraemia after gastric ESD was temporary[9]. Other studies also concluded that prophylactic antibiotics may be unnecessary in gastric ESD patients[8, 10]. Since fever after ESD may be noninfectious, the necessity of antibiotics for fever after ESD is confusing. The aim of this study was to analyse the need for antibiotics for postoperative fever.

Before ESD procedure, patients need complete preopreative examination, including CT, EUS, laboratory examination and so on. Hence, in our study, the median hospitalization is 7 (6–9) in non-antibiotic group and 8 (7–10) antibiotic group. In the present study, the use of antibiotics did not shorten the duration of fever but increased the duration of hospitalization. This was also the case in the subgroup analysis of individuals with a temperature < 38.5 °C. There was no difference in the duration of fever between the patients with a temperature above 38.5 °C who used antibiotics and those who did not use antibiotics, and there was

also no significant difference in the number of days spent in the hospital between the two groups, which may be related to the small sample size. The mechanism of fever development after ESD is not clear. In clinical practice, some doctors will empirically use antibiotics for patients with fever after an ESD operation. However, in this study, the use of antibiotics did not reduce the duration of fever and even increased the duration of hospitalization. In addition, the use of antibiotics will also increase the cost of hospitalization and may cause adverse reactions to antibiotics, such as allergies, drug resistance and secondary infection[16–18]. We hypothesized that pyrexia after ESD is a physiological febrile response similar to that occurring after surgery[19]. The fever may be due to the release of inflammatory cytokines from macrophages, endothelial cells and the reticuloendothelial system after tissue damage, and these cytokines cause the elevation of the thermoregulatory set point for body temperature[20, 21].

Although this was a retrospective study, our research had a large sample size, and we compared the fever duration between patients in the antibiotic and non-antibiotic groups. In addition, we performed PS matching to minimize bias. Importantly, few studies have evaluated the necessity of using antibiotics for fever after ESD.

There were some limitations of the present study. Firstly, the present study was a single-centre retrospective study. The findings of the present study need to be validated by multicentre prospective studies. Secondly, the use of antibiotics was according to the experience of the doctors, which may potentially introduce a source of bias: such as the most severe cases received antibiotics and the mild ones did not. However, this study used PS analysis to control and reduce such bias. Hence, this problem can be neglected.

Conclution

In conclusion, doctors can choose observation treatment and antibiotics should not be used when patients have fever after ESD, for antibiotics may not have much effect on fever after ESD but will increase hospitalization duration.

Abbreviations

ESD
Endoscopic submucosal dissection; PS:Propensity score; EUS:Endoscopic ultrasound; CT:Computerized tomography; APC:Argon plasma coagulation; MP:Muscularis propria; ESE:Endoscopic submucosal excavation; EFTR:Endoscopic full-thickness resection; OTSCs:Over-the-scope clip system; PPIs:Proton pump inhibitors; SD:Standard deviation; IQR:Interquartile range; ASD:Absolute standardized difference.

Declarations

Ethics approval and consent to participate: The study was approved by the ethics committee of The First Affiliated Hospital of Nanchang University. Informed consent by verbal was obtained from all participants approved by the ethics committee.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: All authors declare that they have no competing interests.

Funding: Not applicable.

Author contributions: Lai YK collected the data, analyzed relevant information, and wrote the manuscript; Qian Zhang collected the data; Xiaolin Pan, Zhenhua Zhu, Shunhua Long, Xiaojiang Zhou, Guohua Li, Yin Zhu and Youxiang Chen clinically managed the patient. Shu X clinically managed the patient, designed the article and approved the final submission. All authors read and approved the final manuscript.

Acknowledgments: Not applicable.

Disclosure of potential conflicts of interest: Yongkang Lai, Qian Zhang, Xiaolin Pan, Zhenhua Zhu, Shunhua Long, Xiaojiang Zhou, Guohua Li, Yin Zhu, Youxiang Chen and Xu Shu have no conflicts of interest or financial ties to disclose.

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Tables

Table.1 Clinical characteristics of patients in the study before and after propensity score

		Before Matching				After Matching			
	All	Non-antibiotics(n = 240)	Antibiotics (n = 211)	ASD#	p	Non-antibiotics(n = 96)	Antibiotics (n = 96)	ASD#	p
Age,median (IQR)	54 (46–62)	53 (44–62)	55 (48–63)	0.606	0.047	57 (51–65)	56 (49–64)	0.025	0.384
Gender				0.023	0.509			0.022	0.628
Female	302 (67)	164 (68.3)	138 (65.4)			71 (74)	68 (70.8)		
Male	149 (33)	76 (31.7)	73 (34.6)			25 (26)	28 (29.2)		
Diabetes	16 (3.5)	9 (3.8)	7 (3.3)	0.09	0.804	4 (4.2)	6 (6.3)	0.011	0.519
Hypertension	71 (15.7)	34 (14.2)	37 (17.5)	0.02	0.327	20 (20.8)	20 (20.8)	0.018	1
Previous abdominal surgery	52 (11.5)	27 (11.3)	25 (11.8)	0.016	0.843	10 (10.4)	10 (10.4)	0.015	1
Lesion location				0.039	0.001			0.037	0.924
Upper 1/3 stomach	183 (40.6)	76 (31.7)	107 (50.7)			42 (43.8)	43 (44.8)		
Middle 1/3 stomach	159 (35.3)	87 (36.3)	72 (34.1)			36 (37.5)	35 (36.5)		
Lower 1/3 stomach	109 (24.1)	77 (32.1)	32 (15.2)			18 (18.7)	18 (18.7)		
Median tumor size (mm, IQR)	10 (7–18)	10 (8–18)	10 (6–20)	0.55	0.553	20 (10–25)	20 (10–30)	0.024	0.651
Pathology				0.027	0.217			0.021	0.38
Mucosa / Submucosa	354 (78.5)	183 (76.3)	171 (81)			78 (81.3)	73 (76)		
Muscular layer	97 (21.5)	57 (23.8)	40 (19)			18 (18.7)	23 (24)		
Intraoperative bleeding	157 (34.8)	78 (32.5)	79 (37.4)	0.024	0.272	36 (37.5)	39 (40.6)	0.023	0.657
Perforation	198 (43.9)	54 (22.5)	144 (68.2)	0.022	0.001	47(49)	49 (51)	0.022	0.773
Median operation time(min, IQR)	37 (28–51)	35 (24.25–45.75)	38 (10–58)	0.568	0.001	37 (29–48)	37 (28-53.75)	0.019	0.741
En bloc resection	420 (93.1)	226 (94.2)	194 (91.9)	0.012	0.354	91(94.8)	91 (94.8)	0.012	1
Median maximum body temperature (℃, IQR)	37.7 (37.6–38.1)	37.7 (37.6–38)	38.2 (37.9–38.7)	0.021	0.001	37.8 (37.6–38.1)	37.8 (37.6–38)	0.016	0.58

⍰38.5°C	398 (88.2)	226 (95.36)	172 (81.52)			87 (90.6)	89 (92.7)		
≥38.5°C	53 (11.8)	11 (4.64)	39 (8.48)			9 (9.4)	7 (7.3)		
Stomach tube placement	352 (78)	177 (73.8)	175 (82.9)	0.021	0.019	82 (85.4)	79 (82.3)	0.021	0.557

The absolute standardized difference (ASD) was used to assess the balance of covariates between the two groups.Variables with an ASD > 0.10 is considered to be imbalance

Table 2
Comparison between the two groups (adjustment through PS regression)

	Non-antibiotic	Antibiotic	p
Fever timer*	90.45△	102.55△	0.074
Median hospitalization [days, median(IQR)]	7 (6–9)	8 (7–10)	0.006

* Fever time was recorded as rank variables and comparison was made by Wilcoxon rank sum test; △Average rank.

Table 3
Subgroup analysis of the two groups (adjustment through PS regression)

		Non-antibiotic	Antibiotic	p
⍰38.5 °C	Fever time*	82.55△	94.32△	0.061
	Hospitalization[days, median(IQR)]	7 (6–9)	8 (7–10)	0.009
≥ 38.5 °C	Fever time*	7.39△	9.93△	0.299
	Hospitalization(days, mean ± SD)	7.67 ± 2.29	9.71 ± 1.56	0.455

* Fever time was recorded as rank variables and comparison was made by Wilcoxon rank sum test; △Average rank; Hospitalization(⍰38.5 °C) was abnormal distribution; Hospitalization(≥ 38.5 °C) was normal distribution.

Figures

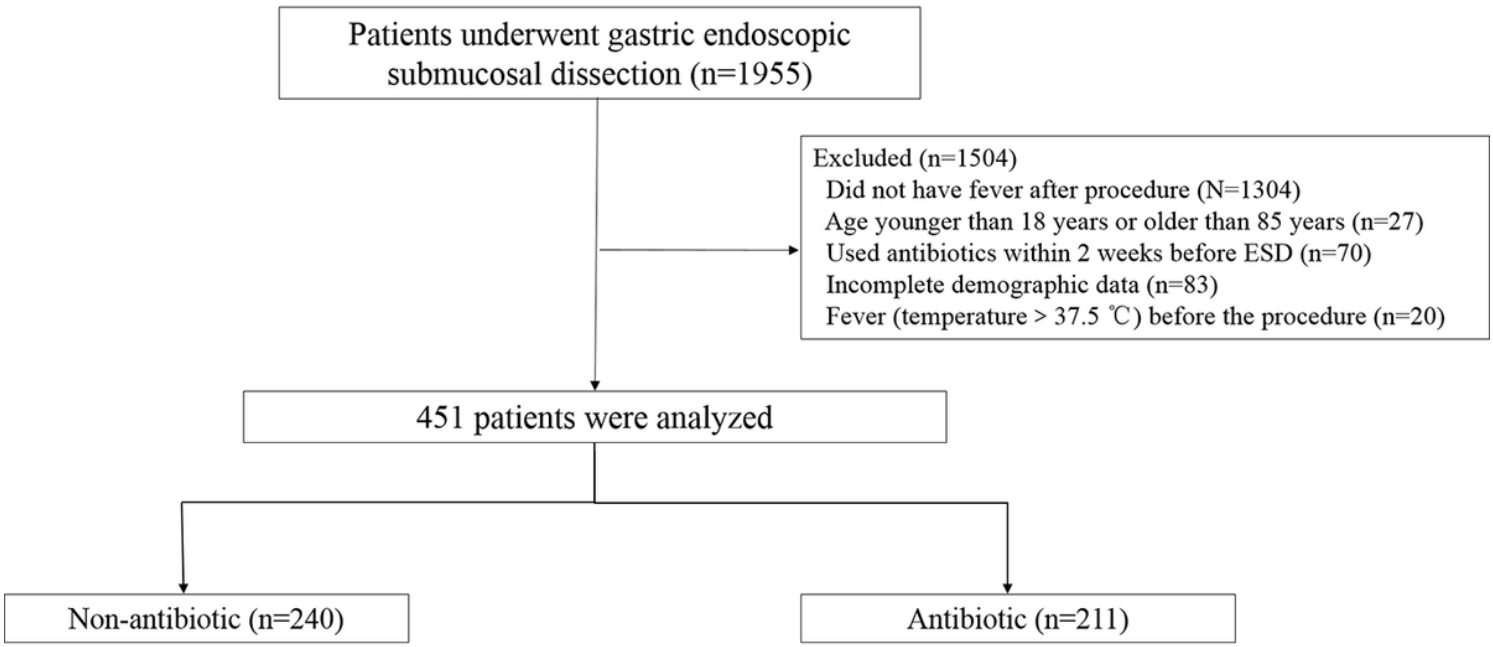

Figure 1

Flowchart of patients included in the present study.

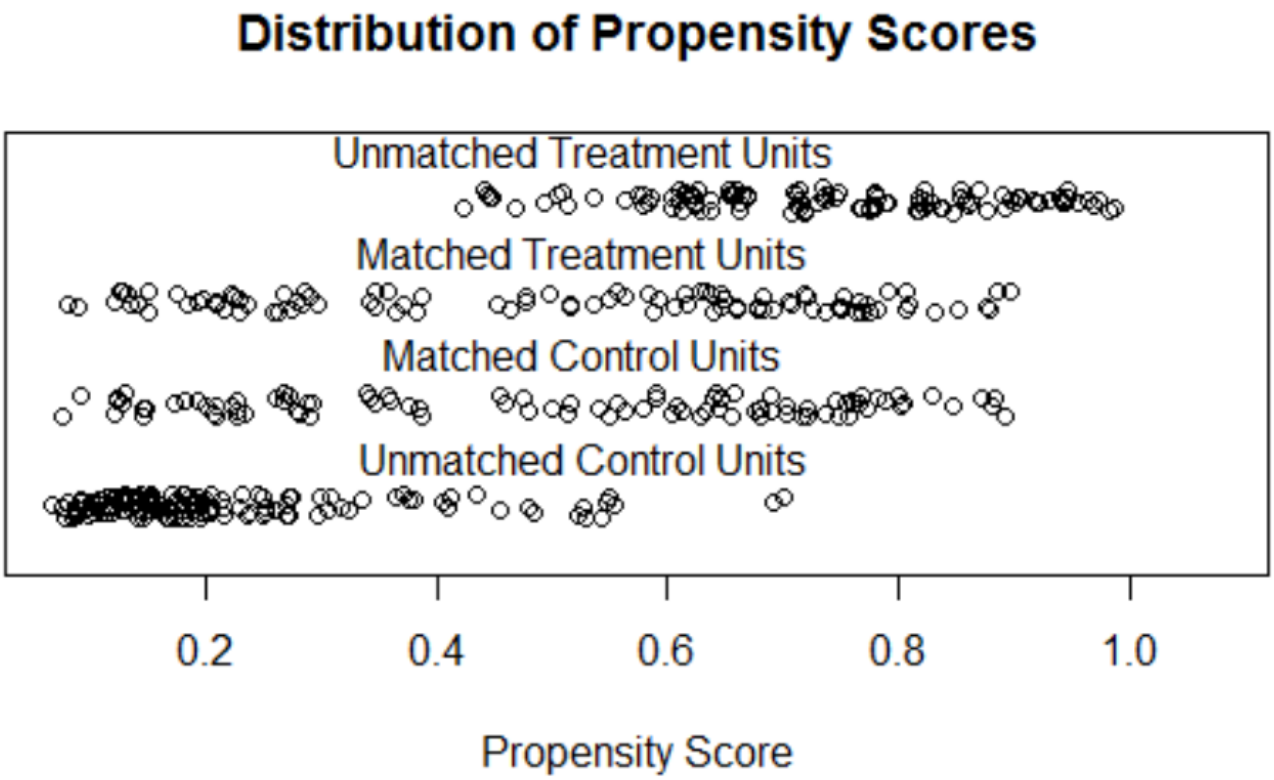

Figure 2

Scatter diagram of tendency distribution before and after matching.

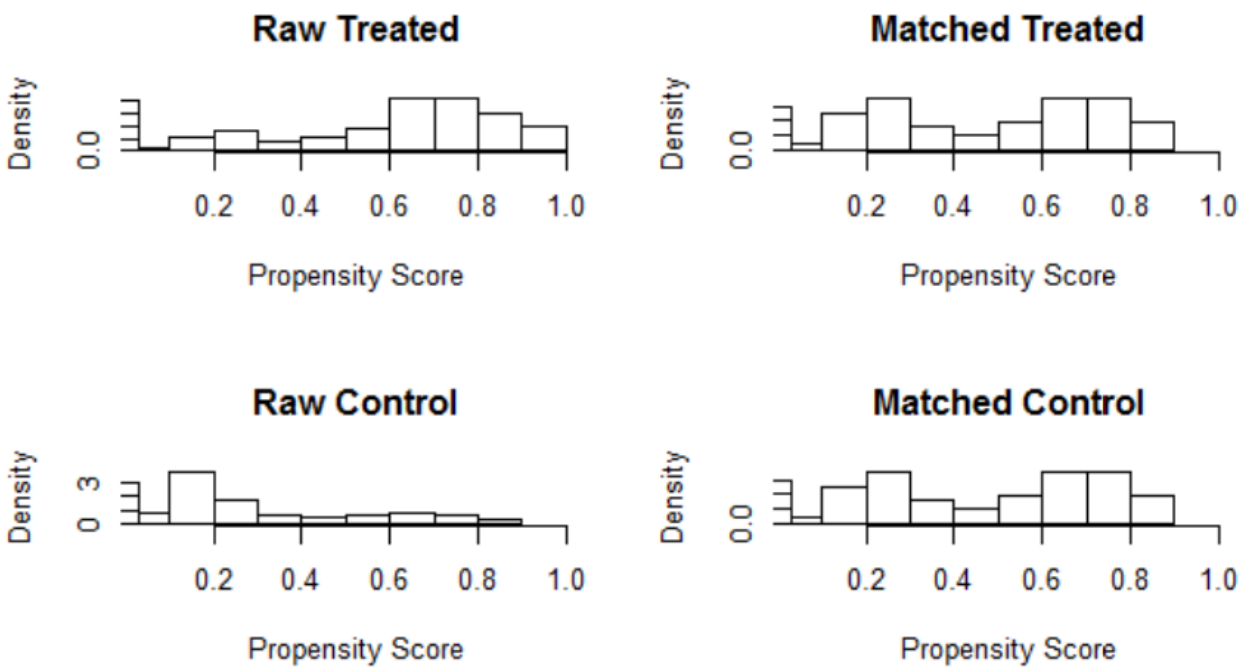

Figure 3

Histogram of tendency distribution before and after matching.