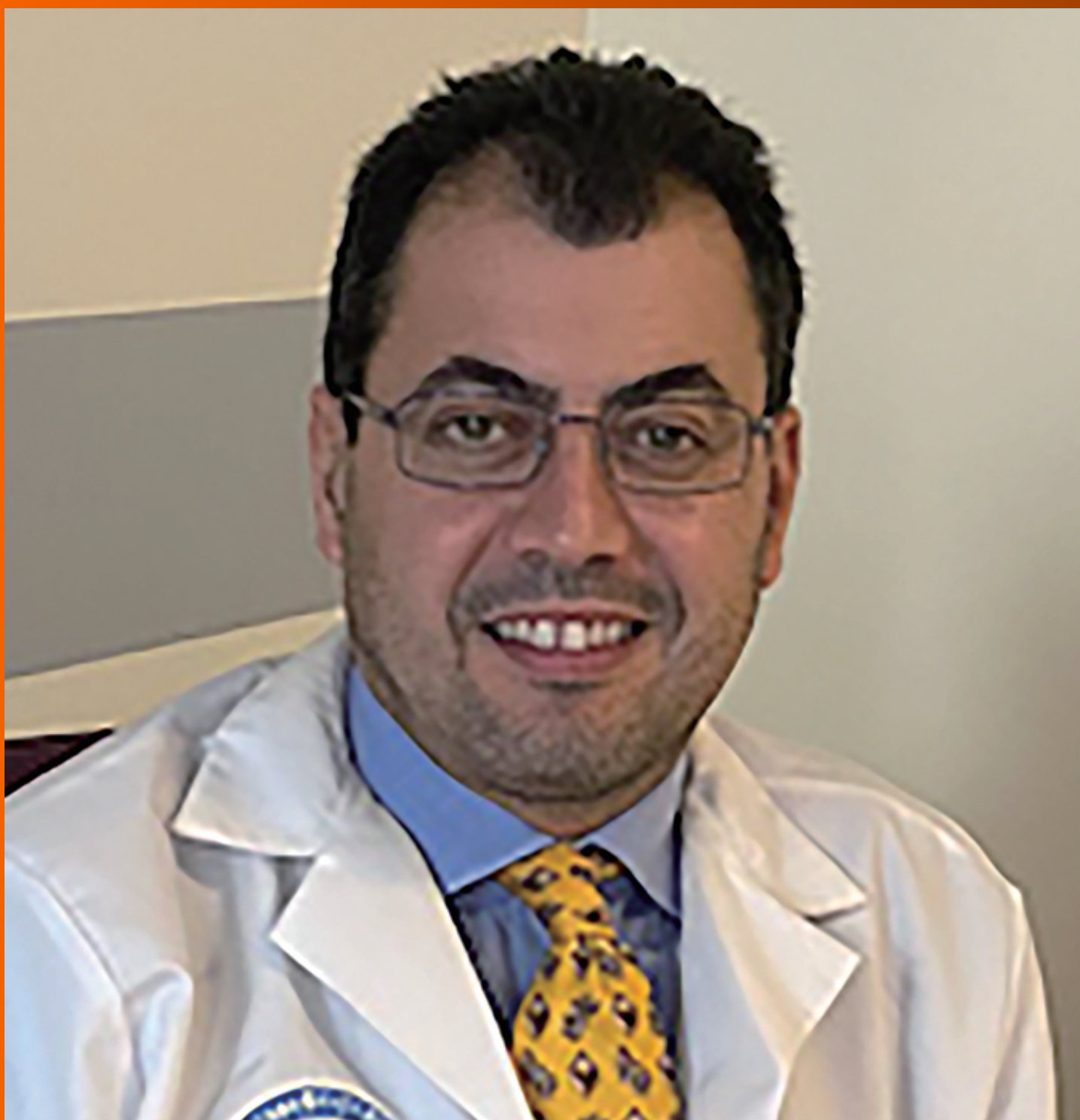


# World Journal of *Gastrointestinal Surgery*

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The WJGS is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for WJGS as 2.582; IF without journal self cites: 2.564; 5-year IF: 3.378; Journal Citation Indicator: 0.53; Ranking: 97 among 212 journals in surgery; Quartile category: Q2; Ranking: 73 among 92 journals in gastroenterology and hepatology; and Quartile category: Q4.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Rui-Rui Wu, Production Department Director: Xiang Li, Editorial Office Director: Ya-Juan Ma.

**NAME OF JOURNAL**

*World Journal of Gastrointestinal Surgery*

**ISSN**

ISSN 1948-9366 (online)

**LAUNCH DATE**

November 30, 2009

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Shu-You Peng, Varut Lohsiriwat

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/1948-9366/editorialboard.htm>

**PUBLICATION DATE**

December 27, 2021

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<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/gerinfo/239>

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## Platelet rich plasma effectiveness in bowel anastomoses: A systematic review

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**Conflict-of-interest statement:** The authors declared no potential conflicts of interest.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript

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### Abstract

#### BACKGROUND

Anastomotic leak constitutes a major problem in abdominal surgery. Technical insufficiency, topical or systemic factors contribute to disrupted healing of the performed bowel anastomosis and result in anastomosis leakage, with detrimental effects on patient postoperative outcomes. Despite the investigation of several factors and the invention of protective materials, the ideal agent to prevent anastomotic leaks is yet to be determined.

#### AIM

To study the effect of platelet rich plasma (PRP) on the healing of bowel anastomoses.

#### METHODS

A systematic literature search was performed in PubMed, EMBASE, and Scopus



was prepared and revised according to the PRISMA 2009 Checklist.

**Country/Territory of origin:** United States

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): 0  
Grade C (Good): C  
Grade D (Fair): 0  
Grade E (Poor): 0

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**Received:** April 19, 2021

**Peer-review started:** April 19, 2021

**First decision:** July 27, 2021

**Revised:** August 11, 2021

**Accepted:** November 18, 2021

**Article in press:** November 18, 2021

**Published online:** December 27, 2021

**P-Reviewer:** Yasukawa K

**S-Editor:** Gao CC

**L-Editor:** A

**P-Editor:** Gao CC



databases to identify studies investigating the effect of PRP application on bowel anastomosis.

## RESULTS

Eighteen studies were eligible with a total population of 712 animals including rats (14 studies), rabbits (2 studies) and pigs (2 studies). No postoperative complications were reported following PRP application. Fourteen out of 18 studies reported a statistically significant higher anastomosis bursting pressure in PRP groups compared to control either in healthy animals or animal models with underlying condition or intervention, such as intraperitoneal chemotherapy or peritonitis. Similar results were reported by ten studies in terms of tissue hydroxyproline levels. One study reported significant increase in collagen deposition in PRP groups. PRP application resulted in significantly decreased inflammatory cell infiltration in the presence of peritonitis or intraperitoneal chemotherapy (6 studies).

## CONCLUSION

The application of PRP is associated with improved bowel anastomosis outcomes, especially in animal models having an underlying condition affecting the normal healing process. PRP application seems to augment the normal healing process under these circumstances. However, further studies are needed to investigate the potential role of PRP on bowel anastomosis healing, especially in clinical settings.

**Key Words:** Platelet rich plasma; Colonic anastomosis; Small bowel anastomosis; Large bowel anastomosis; Bowel anastomosis; Surgery

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**Core Tip:** The positive effect of platelet rich plasma (PRP) in bowel anastomoses has been shown by several studies. The application of PRP in bowel anastomoses in the presence of impaired wound healing conditions like ischemia, infection or chemotherapy significantly improved anastomosis burst pressure and tissue hydroxyproline, two of the most common used parameters to test anastomosis integrity. The current literature supports the effectiveness of PRP in animal models. Further studies are needed in order to determine the potential role of PRP in clinical practice.

**Citation:** Geropoulos G, Psarras K, Giannis D, Martzivanou EC, Papaioannou M, Kakos CD, Pavlidis ET, Symeonidis N, Koliakos G, Pavlidis TE. Platelet rich plasma effectiveness in bowel anastomoses: A systematic review. *World J Gastrointest Surg* 2021; 13(12): 1736-1753

**URL:** <https://www.wjgnet.com/1948-9366/full/v13/i12/1736.htm>

**DOI:** <https://dx.doi.org/10.4240/wjgs.v13.i12.1736>

## INTRODUCTION

Bowel anastomosis related complications are frequently encountered in patients undergoing major abdominal surgery involving bowel excision. Anastomotic leak seems to be the most common complication and its rate is approximately 10% in operations involving bowel anastomosis[1-4]. However, in the presence of an underlying condition, such as malignancy or intraperitoneal hyperthermic chemotherapy, an anastomotic leak may occur in up to 25% of the cases[5-7]. Multiple factors have been previously investigated and have been proven to affect the integrity of bowel anastomosis. Advanced age, sepsis, hypoalbuminemia, low hematocrit, immunosuppression, diabetes mellitus, and reduced blood supply are systemic factors that may negatively affect anastomotic healing[8,9]. In addition, topical factors, including suturing technique, anastomotic tension, bowel infection, fecal contamination and peritonitis, could also result in delayed healing and increase the rate of anastomotic leak[10].

Several topical mechanical and pharmaceutical agent applied to bowel anastomosis have been reported in the literature, demonstrating variable effects in the healing process of anastomoses. The vast majority of these agents have been tested in experimental animal (mainly rat) models. However, very few agents were applied to the clinical practice[9].

Platelet rich plasma (PRP) is widely used in maxillofacial reconstructive surgery, orthopedic surgery, plastic surgery, and diabetic skin ulcers with highly acceptable effects in terms of improved wound healing and tissue regeneration[11-13]. PRP is easily extracted from a small amount of peripheral blood and its production roughly requires a two-step centrifugation or even a one-step centrifugation technique[14]. The effects of PRP are mainly attributed to its endogenous concentration of growth factors, including platelet-derived growth factor (PDGF), transforming growth factor- $\beta$  (TGF- $\beta$ ), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), hepatocyte growth factor, and insulin-like growth factor (IGF)[15]. Furthermore, inflammatory biomolecules like interleukin (IL)-1 $\beta$ , IL-6 and IL-4 have been also reported in the PRP biochemical analysis[16].

The synergic effect of these factors modulates and/or augments angiogenesis, cell mitosis and extracellular matrix remodeling, which are processes involved in normal wound healing[17-19].

The aim of this study is to systematically review the current literature on the effects of PRP application on bowel anastomosis.

## MATERIALS AND METHODS

### Search strategy

This systematic review was performed according to the PRISMA guidance[20] after approval of the study protocol by all authors. A comprehensive literature search (last search date as of October 1, 2020) was performed by two researchers (Kakos CD and Martzivanou EC) in PubMed (Medline), EMBASE, and Scopus. The search term included several combinations of “platelet rich plasma”, “PRP”, “colon” and “anastomosis” keywords (Supplementary Table 1). A manual search was also performed using the snowball methodology to identify any relevant studies in the list of references of the included articles[21].

### Study selection process

Our systematic review included retrospective animal studies that investigated the effect of PRP on bowel anastomosis. There was no restriction regarding the animal models that were used and these included healthy animals as well as animals with peritonitis or undergoing intraperitoneal chemotherapy. Studies were excluded based on the following criteria: (1) Non-available full texts; (2) Non-peer reviewed publications, including theses, conference papers, and book chapters; (3) Non-original studies, such as systematic reviews and narrative reviews; (4) Studies with non-extractable data; and (5) Studies with overlapping or duplicated data.

### Data extraction

A data extraction template was created and modified based on an initial pilot testing. Three investigators (Kakos CD, Martzivanou EC and Geropoulos G) independently identified and extracted the variables of interest. Extracted variables included study details (author, year, country, study type), animal type, underlying animal condition, study subgroups, origin of PRP, preparation method of PRP, dose of PRP, PRP application technique, type of anastomosis, interval between PRP application and animal sacrifice, postoperative complications, postoperative outcomes (bursting pressure, hydroxyproline levels, adhesions) and histopathology results (inflammatory cell infiltration, necrosis, angiogenesis, edema, collagen deposition, fibrosis, fibroblast count, anastomotic epithelialization, granulation). Any discrepancies between the results of extraction were discussed and resolved, while a fourth investigator (Giannis D) was consulted if needed.

### Quality assessment

The risk of bias of included studies was evaluated with the Systematic Review Centre for Laboratory animal Experimentation risk of bias tool (SYRCLE's RoB tool)[22]. The quality assessment tool is based on the Cochrane Risk Of Bias tool, but it is adjusted to estimate the risk of bias in animal/preclinical studies. Each question is answered as

“yes” (low risk of bias), “no” (high risk of bias), or “unknown” (unknown/unclear risk of bias). Two authors (Martzivanou EC and Geropoulos G) independently assessed the 10 components of the SYRCLE's RoB tool. Any conflicts were resolved by discussion with a third investigator (Giannis D).

## RESULTS

### *Literature search, included studies and selection process*

Among the 3858 studies that were identified, 2407 were screened after removal of duplicates, through the use of Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia) and manual screening of titles and abstracts[23]. According to the predefined inclusion and exclusion criteria, 26 studies were selected for full text screening. Eventually, eight studies were excluded (four studies not describing the effect of PRP on bowel anastomosis, one duplicate study published in two different journals[24,25], one comment paper, one conference paper and one letter to the editor without extractable data. After manual literature search in the references of the eligible studies, which did not provide any additional eligible studies, 18 studies were finally included in this systematic review (Figure 1). Two out of the 18 included studies investigated the effect of platelet rich fibrin (PRF), which is similar to PRP in terms of high platelet concentration. However, PRF is rich in fibrin, which is thought to trap platelets and ease the application around the anastomotic surface[16,26] (Table 1).

### *Surgical procedure*

The majority of the studies (12 studies) investigated the effect of PRP on colonic anastomosis, while six studies investigated the effect on small bowel anastomosis[16, 18,19,25,27]. End-to-end anastomosis was performed to restore the bowel continuity in all included studies. Concurrent bowel resection was reported in three studies[16,28, 29]. Suturing method was continuous in four studies[16,17,28,29] or simple interrupted in six studies[18,19,30-33]. Circular stapler was used in one study[26].

### *PRP origin, pharmacokinetics and method of application*

The origin of PRP was homologous or autologous. Autologous PRP was used in three rat studies[9,10,34], two rabbit studies[25,27] and three pig studies[19,26,28]. Daglioglu *et al*[9] and Özçay *et al*[16], in the autologous PRP group, extracted 2.5 mL and 1 mL from each rat, respectively, while Yol *et al*[10] did not report the amount of blood taken from each rat. In the pig and rabbit groups, a total of 60-100 mL and 8-10 was taken, respectively. All ten studies that investigated the effect of homologous PRP were conducted on rats[17,18,29-36] and the number of rat donors ranged from five to twelve rats, while the amount of blood drawn from each donor ranged between 5-10 mL. A two-step centrifugation technique was applied in 16 studies investigating PRP. Dauser *et al*[26] utilized a specific kit for the preparation of PRF, while Özçay *et al*[16] used an one step centrifugation technique to extract PRF.

Direct application of PRP on bowel anastomosis was mentioned in 13 studies[9,10, 16,18,26,29-36], merging of the bowel edges with PRP enriched material in three studies[19,25,28], PRP injection adjacent to anastomosis in one study[25], and anastomosis performed with PRP coated sutures in two studies[17,27]. Lastly, two studies investigated PRP pharmacokinetics[18,27]. PDGF subunit A release to the media from PRP coated sutures was stable and showed no significant changes at 1, 2, 24 and 48 h post application. Similarly, the release of TGF- $\beta$ 1 was increased significantly in the first hour, but thereafter the release was stable without any major changes[27]. PDGF-BB and TGF- $\beta$ 1 showed statistically significant higher concentration in the high concentration PRP *vs* low concentration PRP and platelet poor plasma groups[18].

### *Postoperative outcomes and complications*

In total, eight deaths were reported and included one death in the PRP group[9] and seven deaths in the comparison groups. No postoperative complications related to PRP were reported among the included studies.

Common anastomosis related parameters measured among the included studies are the anastomotic bursting pressure, tissue hydroxyproline, collagen deposition and inflammatory cell infiltration. These results are summarized in Table 2. The comparison and the associated statistical significance of PRP, control and other agents



Table 1 Basic characteristics of the included studies

Ref.	Country	Animal model (race)	Sample size (n)	Number of groups (n)	Animal per group (n)	Day at animal sacrifice	Underlying animal condition that PRP was tested	PRP amount in anastomosis (and factors mixed with PRP)	Control	Primary comparison
Daglioglu <i>et al</i> [9], 2018	Turkey	Rat (Winstar-Albino)	36	3	12	Day 7	Normal	0.5 mL PRP	Simple end-end colon anastomosis	PRP <i>vs</i> fibrin glue
Ocak <i>et al</i> [34], 2019	Turkey	Rat (Winstar-Albino)	35	3	10	Day 7	Hyperthermic intraperitoneal chemotherapy (HIPEC)	200 µL PRP (200 µL thrombin and 100 µL calcium solution)	Hyperthermic saline after anastomosis	PRP <i>vs</i> non PRP application in rats having HIPEC with cisplatin
Yol <i>et al</i> [10], 2008	Turkey	Rat (Sprague Dawley)	30	3	10	Day 7	Normal	1 mL PRP (0.1 mL thrombin and 1 mL calcium solution)	Simple end-end colon anastomosis	PRP <i>vs</i> bioglu
Buk <i>et al</i> [35], 2020	Turkey	Rat (Winstar-Albino)	35	3	10	Day 7	HIPEC	1 mL PRP (1 mL thrombin and 0.5 mL calcium solution)	Hyperthermic saline after anastomosis	PRP <i>vs</i> non PRP application in rats having HIPEC with oxaliplatin
Dzhumabekov <i>et al</i> [25], 2019	Kazakhstan	Rabbit (Chinchillas)	81	3	27	Day 7	Normal	0.2 mL/m <sup>2</sup> PRP	Normal saline injected in the muscular layer of end-end small bowel anastomosis	PRP injection in bowel muscular layers <i>vs</i> soaking of bowel edges in PRP before anastomosis
Aydin <i>et al</i> [17], 2020	Turkey	Rat (Sprague Dawley)	24	3	8	Day 7	Normal	0.7 µL PRP absorbed by sutures	Simple end-end colon anastomosis	Higher <i>vs</i> lower platelet concentration PRP-impregnated vicryl sutures
Dauser <i>et al</i> [26], 2020	Austria	Pig	16	4	4	Day 0, 4, 10 and 30	Normal	PRF spray	Each group had one animal as a control: A simple anastomosis was performed with a circular stapler	PRF <i>vs</i> no PRF application tested in several postoperative days
Giusto <i>et al</i> [28], 2017	Italy	Pig (Landace X Large White)	8	2	4	Day 8	Normal	1 mL PRP (50 µL calcium solution)	2 out of 6 anastomoses performed in each animal used as a control anastomosis [no PRP or platelet rich in growth factors (PRGF) applied]	PRP <i>vs</i> PRGF
Zhou <i>et al</i> [29], 2014	China	Rat (Sprague Dawley)	30	3	10	Day 7	Open abdomen. A polypropylene mesh used for abdomen closing in the open abdomen group	1 mL PRP	Simple end-end colon anastomosis	PRP <i>vs</i> non PRP application in a background of open abdomen
Göksu <i>et al</i> [30], 2020	Turkey	Rat (Wistar Albino)	24	3	8	Day 7	HIPEC	PRP alone (dose not mentioned)	Hyperthermic saline after anastomosis	PRP <i>vs</i> non PRP application in rats having HIPEC with 5-fluorouracil (5-FU)
Özçay <i>et al</i> [16], 2018	Turkey	Rat (Sprague Dawley)	40	4	10	Day 7	Mesenteric ischemia/reperfusion injury (IR injury)	PRF membrane applied around the anastomosis	Simple end-end colon anastomosis	PRF <i>vs</i> non PRF application following IR injury
Fresno <i>et al</i> [19],	Spain	Pig (White)	35	7	3 or 10	Day 1, 2, 3, 4	Normal	1 mL PRP (50 µL	1 out of 2 anastomoses performed	PRP effect on several

2010						and 7		calcium solution)	in each animal used as a control anastomosis (no PRP or PRGF applied)	postoperative days
Daradka <i>et al</i> [27], 2019	Jordan	Rabbit (mixed-breed)	30	3	10	Day 3 and 10	Normal	Sutures submerged in 1 ml PRP solution	Simple end-end ileal anastomosis	PRP <i>vs</i> sodium citrate coated sutures
Yalı <i>et al</i> [36], 2020	Turkey	Rat (Wistar-Albino)	56	4	12	Day 5	Peritonitis	1 mL PRP (1 mL calcium solution)	Simple end-end colon anastomosis	PRP in normal abdomen <i>vs</i> peritonitis
Pehlivanli <i>et al</i> [33], 2019	Turkey	Rat (Wistar Albino)	55	5	10	Day 10	Mesenteric ischemia	1 mL PRP	Simple end-end colon anastomosis	PRP <i>vs</i> Zeolite <i>vs</i> thymoquinone
Sozutek <i>et al</i> [31], 2016	Turkey	Rat (Wistar Albino)	50	4	10	Day 7	Peritonitis	1 mL PRP (1 mL thrombin and 50 µL calcium solution)	Simple end-end colon anastomosis	PRP in normal abdomen <i>vs</i> peritonitis
Yamaguchi <i>et al</i> [18], 2012	Japan	Rat (Sprague-Dawley)	77	4	12	Day 5	Normal	180 µL PRP (180 units of bovine thrombin and 30 µL of calcium solution).	Simple end-end colon anastomosis	Platelet poor plasma <i>vs</i> low <i>vs</i> high platelet rich plasma
Gorur <i>et al</i> [32], 2020	Turkey	Rat (Wistar Albino)	50	4	10	Day 7	Intraperitoneal administration of 5-FU	1 mL PRP (1 mL thrombin and 50 µL of calcium solution)	Simple end-end colon anastomosis	PRP <i>vs</i> non PRP application in rats having intraperitoneal administration of 5-FU

PRP: Platelet rich plasma.

are presented with the related *P* value. Other reported outcomes are described subsequently.

### Macroscopic findings

Intrabdominal adhesions were assessed in five studies[16,25-28]. Soaking of the bowel edges in PRP resulted in increased formation of intrabdominal adhesions compared to the injection of PRP along the anastomosis line and compared to the control group [25]. Compared to the platelet rich in growth factors (PRGF) and control groups, the use of PRP resulted in a non-significantly increased formation of intrabdominal adhesions[28]. In another technique, suture soaking in PRP material was associated with significantly lower adhesion scores in the anastomotic sites in a rabbit animal model[27]. Dauser *et al*[26], reported that the application of PRF was not associated with significant changes in adhesion formation, compared to the control group. In contrast, Özçay *et al*[16] reported that the application of PRF resulted in significantly decreased formation of intra-abdominal adhesions in the ischemia/reperfusion injury animal model compared to the non PRF groups[16].

### Circulating inflammatory markers and immunohistology changes

Daglioglu *et al*[9], reported no statistically significant changes in proinflammatory

**Table 2 Anastomotic burst pressure, tissue hydroxyproline, collagen deposition and inflammatory cell infiltration**

Ref.	Anastomotic burst pressure (mm/hg)				Tissue hydroxyproline (µg/mg)				Collagen deposition	Inflammatory cells deposition
	PRP	Control	Other agent	P value	PRP	Control	Other agent	P value		
Daglioglu <i>et al</i> [9], 2018	146 ± 44.55 mm/hg	119 ± 35.65 mm/hg	149.1 ± 72.29 mm/hg (Fibrin glue)	<i>vs</i> Control (0.026); <i>vs</i> Fibrin glue (0.896)	120.1 ± 51.5 µg/mg	96.2 ± 29.22 µg/mg	118.71 ± 42.18 µg/mg	<i>vs</i> Control (0.023); <i>vs</i> Fibrin glue (0.745)	No significant difference between groups	No significant difference between groups
Ocak <i>et al</i> [34], 2019	146 ± 21.85 mm/hg	180 ± 9.14 mm/hg	115.8 ± 18.19 mm/hg (HIPEC with cisplatin group)	<i>vs</i> Control (< 0.001); <i>vs</i> HIPEC with cisplatin (0.01)	256.59 ± 84.03 ng/mg	314.69 ± 47.56 ng/mg	148.02 ± 26.57 ng/mg (HIPEC with cisplatin)	<i>vs</i> Control (0.335); <i>vs</i> Hyperthermic saline group (< 0.001)	-	Inflammatory cell infiltration is significant decreased with PRP application in HIPEC and cisplatin model
Yol <i>et al</i> [10], 2008	270 ± 29.8 mm/hg	195 ± 15.3 mm/hg	214 ± 16.46 mm/hg (bioglue)	<i>vs</i> Control (< 0.001); <i>vs</i> Bioglue (< 0.001)	18.2 ± 4.95 µg/mg	10.96 ± 5.94 µg/mg	11.08 ± 5.08 µg/mg	<i>vs</i> Control (0.016); <i>vs</i> Bioglue (0.026)	Rich collagen production was observed in the PRP group. No comparison between groups	Less inflammatory cell infiltration in the PRP group
Buk <i>et al</i> [35], 2020	125.7 ± 15.64 mm/hg	180 ± 9.14 mm/hg	94.90 ± 9.9 mm/hg (HIPEC with oxilipatin)	<i>vs</i> Control (< 0.001); <i>vs</i> HIPEC with oxilipatin group (< 0.001 <sup>1</sup> )	280.92 ± 45.85 ng/mg	314.69 ± 75.57 ng/mg	92 ± 26.97 ng/mg (HIPEC with oxilipatin)	<i>vs</i> Control (< 0.001); <i>vs</i> HIPEC with oxilipatin (< 0.001 <sup>1</sup> )	-	Inflammatory cell infiltration is significant decreased with PRP application in oxilipatin model
Dzhumabekov <i>et al</i> [25], 2019	1.76 ± 0.28 (PRP soaking group) <sup>1</sup>	1.54 ± 0.23 <sup>1</sup>	1.81 ± 0.17 <sup>1</sup> (PRP injecting group)	<i>vs</i> Control (0.05); <i>vs</i> PRP injecting group (0.69)	-	-	-	-	No significant differences between groups	Inflammatory cell infiltration significantly lower in the PRP soaking or injection group
Aydin <i>et al</i> [17], 2020	121 ± 57 mm/hg	124 ± 61 mm/hg	180 ± 49 mm/hg (low concentration PRP)	<i>vs</i> Control (> 0.05); <i>vs</i> low concentration PRP (< 0.001 <sup>1</sup> )	0.39 ± 0.10 µg/mg	0.25 ± 0.17 µg/mg	0.56 ± 0.37 µg/mg (low concentration PRP)	<i>vs</i> Control (< 0.001); <i>vs</i> low concentration PRP (< 0.05 <sup>1</sup> )	-	No significant difference between groups
Dauser <i>et al</i> [26], 2020	Median = 210 mm/hg (day 10)	Median = 60 mm/hg (day 10)	-	The study reports no statistically significant changes between groups due to small sample size	-	-	-	-	Matrix treated animals showed less immature collagen deposition (type III) compared to the control group (day 10). However no significant differences were observed	No significant changes in the M2 or non-M2 macrophage density in the mucosal, mural and serosal layers. No significant changes in inflammatory cell infiltration
Giusto <i>et al</i> [28], 2017	117.5 mm/hg (range: 80-190)	154 mm/hg (range: 50-180)	165 mm/hg (range: 100-190) (PRGF); And 175 mm/hg (range: 160-190) (intact bowel)	<i>vs</i> Control or PRGF (> 0.05); <i>vs</i> Intact bowel (0.0007 <sup>1</sup> )	-	-	-	-	No significant difference between groups	No significant difference between groups
Zhou <i>et al</i> [29], 2014	177 ± 6.95 mm/hg	184.8 ± 6.6 mm/hg	158 ± 5.08 mm/hg (open abdomen group without PRP application)	<i>vs</i> Control (0.398); <i>vs</i> non-PRP application in open abdomen (0.041)	399.7 ± 9.46 µg/mg	403.6 ± 8.55 µg/mg	353.5 ± 6.75 µg/mg (open abdomen group without PRP application)	<i>vs</i> Control (0.74); <i>vs</i> non-PRP application in open abdomen (0.001)	Significantly higher in the PRP and control group	No significant differences between groups

Göksu <i>et al</i> [30], 2020	143 ± 17.35 mm/hg	150 ± 20.49 mm/hg	119.38 ± 17.65 mm/hg (5-FU HIPEC without PRP application)	<i>vs</i> Control (0.718); <i>vs</i> non-PRP 5-FU HIPEC (0.047)	253.64 ± 5.35 µg/mg	259.6 ± 7.95 µg/mg	244.04 ± 7.28 µg/mg (5-FU HIPEC without PRP application)	<i>vs</i> Control (0.224); <i>vs</i> non-PRP 5-FU HIPEC (0.03)	-	Decreased lymphocytes in the PRP compared to the other groups. No statistically significant changes in neutrophil infiltration
Özçay <i>et al</i> [16], 2018	198.1 ± 36.5 mm/hg	205.1 ± 41.1 mm/hg	106.1 ± 33.9 mm/hg (IR injury without PRF)	<i>vs</i> Control (> 0.05); <i>vs</i> non PRF in IR injury (< 0.01)	-	-	-	-	Moderate to severe collagen deposition in all groups but no significant changes between groups	Moderate to severe cellular infiltration but no significant changes between groups
Fresno <i>et al</i> [19], 2010	1.34 ± 0.07 kgf <sup>1</sup> (day 3); 1.14 ± 0.11 kgf <sup>1</sup> (day 7)	1.21 ± 0.08 kgf <sup>1</sup> (day 3); 1.08 ± 0.08 kgf <sup>1</sup> (day 7)	1.8 ± 0.08 kgf <sup>1</sup> (normal tissue)	<i>vs</i> Normal tissue (< 0.05); <i>vs</i> Control day 3 or 7 (> 0.05)	-	-	-	-	No significant difference between groups	-
Daradka <i>et al</i> [27], 2019	60.2 ± 5.5 mm/hg	54.5 ± 7.5 mm/hg	55.6 ± 10.2 mm/hg (sodium citrate coated sutures)	<i>vs</i> Control (0.211)	0.76 ± 0.1 µg/mg	0.47 ± 0.13 µg/mg	0.52 ± 0.07 µg/mg (sodium citrate- coated sutures)	<i>vs</i> Control (< 0.05) on day 10; <i>vs</i> Control (> 0.05) on day 3	Statistically significant higher collagen deposition compared to uncoated suture groups on day 10	Statistically significant less inflammatory infiltration compared to PRP uncoated suture groups
Yalı <i>et al</i> [36], 2020	129.66 ± 26.6 mmH2O	143.25 ± 37.47 mmH2O	154.9 ± 27.64 mmH2O (colon anastomosis in peritonitis) and 173.5 ± 29.49 mmH2O (colon anastomosis and PRP application in peritonitis)	<i>vs</i> Control (> 0.05); <i>vs</i> Colon anastomosis and PRP application in peritonitis (< 0.05)	-	-	-	-	Statistically significant higher collage storage values in PRP treated group compared to control and peritonitis model	Statistically significant differences between groups in terms of inflammatory reaction
Pehlivanli <i>et al</i> [33], 2019	225 (range: 180-250) <sup>2</sup>	200 (range: 90-230) <sup>2</sup>	235 (range: 220-250) <sup>2</sup> thymoquinone; 132.5 (range: 85-150) <sup>2</sup> Zeolite	<i>vs</i> Control (> 0.05); <i>vs</i> Zeolite (< 0.05); <i>vs</i> Thymoquinone (> 0.05)	613.22 (range: 158.55-801.82) <sup>2</sup>	371.27 (range: 164.51-785.45) <sup>2</sup>	473.03 (range: 215.33-963.43) <sup>2</sup> thymoquinone; 459.15 (range: 182.44-738.21) <sup>2</sup> Zeolite	<i>vs</i> Control (> 0.05); <i>vs</i> Zeolite (> 0.05); <i>vs</i> Thymoquinone (> 0.05)	-	No significant difference in terms of inflammation at the anastomotic line in between groups
Sozutek <i>et al</i> [31], 2016	209 ± 14.4 mm/hg	179.5 ± 10.3 mm/hg	129.3 ± 14.2 mm/hg (colon anastomosis in peritonitis); 167.5 ± 7.5 mm/hg (colon anastomosis and PRP application in peritonitis)	<i>vs</i> Control (0.01); <i>vs</i> Colon anastomosis in peritonitis (0.01); <i>vs</i> Colon anastomosis and PRP application in peritonitis (0.01)	17.4 ± 1.21 µg/mg	10.8 ± 0.67 µg/mg	8.98 ± 1.04 µg/mg (colon anastomosis in peritonitis); 10.6 ± 0.52 µg/mg (colon anastomosis and PRP application in peritonitis)	<i>vs</i> Control (0.023); <i>vs</i> Colon anastomosis in peritonitis (0.01); <i>vs</i> Colon anastomosis and PRP application in peritonitis (0.012)	Application of PRP in peritonitis group did no increase collagen deposition significantly	Macrophages significantly increased in PRP <i>vs</i> control group and lymphocytes were significantly decreased in PRP + peritonitis compared to peritonitis group
Yamaguchi <i>et al</i> [18], 2012	148 ± 25 mm/hg (H-PRP)	171 ± 20 mm/hg	174 ± 23 mm/hg (PPP); 189 ± 17 mm/hg (L-PRP)	<i>vs</i> Control (< 0.05); <i>vs</i> L-PRP (< 0.05); <i>vs</i> PPP (< 0.05)	407 ± 143 µg/mg	515 ± 130 µg/mg	495 ± 123 µg/mg (PPP); 629 ± 120 µg/mg (L-PRP)	<i>vs</i> Control (< 0.05); <i>vs</i> L-PRP (< 0.05); <i>vs</i> PPP (< 0.05)	In L-PRP more collagen deposition in the serosa layer compared to other groups. H-PRP showed the lesser collagen deposition compared to other groups	-
Gorur <i>et al</i> [32],	246.7 ± 25.1	232.6 ± 19.5	127.5 ± 17.7 mm/hg	<i>vs</i> Control (> 0.05); <i>vs</i>	1939.5 ±	2994.6 ±	591 ± 84.4 µg/mg (colon	<i>vs</i> Control (0.212); <i>vs</i>	Increased but no	No significant differences

2020	mm/hg	mm/hg	(colon anastomosis and 5-FU intraperitoneal); 202.9 ± 28.8 mm/hg (colon anastomosis + PRP and 5-FU intraperitoneal)	Colon anastomosis and 5-FU intraperitoneal (< 0.05); Colon anastomosis + PRP <i>vs</i> non PRP and 5-FU intraperitoneal (< 0.05)	586 µg/mg	2132.4 µg/mg	anastomosis and 5-FU intraperitoneal); 1171 ± 301.7 µg/mg (colon anastomosis + PRP and 5-FU intraperitoneal)	Colon anastomosis and 5-FU intraperitoneal (< 0.05); Colon anastomosis + PRP <i>vs</i> non PRP and 5-FU intraperitoneal (< 0.05)	statistically significant collagen deposition in colon anastomosis + PRP <i>vs</i> non PRP on a background of intraperitoneal 5-FU administration	between groups
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<sup>1</sup>Breaking strength: Minimal force required for anastomosis rupture.

<sup>2</sup>Anastomotic bursting pressure and tissue hydroxyproline units not reported.

5-FU: 5-Fluorouracil; HIPEC: Hyperthermic intraperitoneal chemotherapy; IR injury: Ischemia/reperfusion injury; PRF: Platelet rich fibrin; PRGF: Platelet rich in growth factors; PRP: Platelet rich plasma.

cytokines IL-6, IL-10 and procalcitonin levels between the PRP and control groups. Higher circulating tumor necrosis factor- $\alpha$  and IL-1b levels in the PRP compared to the control group were observed by Pehlivanli *et al*[33].

Table 2 summarizes the collagen deposition and inflammatory cell infiltration in the PRP treated groups compared to the control or other agents that were also tested. Table 3 describes the results of the Verhofstad histopathology scale that was recorded by some of the included studies. The Verhofstad histopathology scale is used to analyze wound healing by assessing on a 0-3 scale the necrosis, polymorphonuclear leukocytes, macrophages, edema, mucosal epithelium and submucosal-muscular layer healing[37].

Dauser *et al*[26] reported no significant difference in the PRF compared to the control group in terms of foreign body reactivity, mucosal regeneration and inflammatory cell infiltrates. Anastomotic thickness, mean mucin percentage, and microvascular density (at day 30 postoperatively) were also non-significantly increased in the PRF treated anastomosis. The application of PRF was associated with bacterial colonization and infiltration of neutrophils at day 4 in all animals. Both Özçay *et al*[16] and Dauser *et al*[26] did not observe residual PRF material on day 10 and day 30 postoperatively. In contrast, PRP material was visualized in the anastomosis microscopic examination as an eosinophilic material[19]. Epithelialization, cellular infiltration, fibroblast proliferation, and neovascularization did not present a significant increase in the PRF group in the ischemia/reperfusion injury animal model [16]. Staining for the endothelium specific Factor VIII did not present significant changes in the PRP compared to control groups[19].

On postoperative days 1, 2, 3, and 7, Dzhumabekov *et al*[25] studied the fiber-crypt index, intraepithelial lymphocyte count, epithelial-stromal coefficient and mitosis count (mitosis observed outside lymphoid follicles). Higher mitosis rate in the mucosal crypt area was observed in the PRP injection group compared to PRP soaking and control groups on postoperative days 3 and 7. Epithelial-stromal coefficient decreased in the control group. Intraepithelial lymphocyte infiltration did not present any significant difference between groups[25].



Table 3 Verhofstad histopathology scale

Groups	Necrosis	Neutrophil	Lymphocyte	Macrophages	Oedema	Mucosal epithelium	Submucosal layer	Bridging	Total
<i>Ocak et al</i> [34]									
Control	2.3 ± 0.82	2.5 ± 0.52	2.5 ± 0.52	2.5 ± 0.52	2.9 ± 0.31	2.6 ± 0.966	0.8 ± 0.63	-	-
PRP	2.6 ± 0.69	2.8 ± 0.42 <sup>a</sup>	2.7 ± 0.48 <sup>a</sup>	2.7 ± 0.48 <sup>a</sup>	2.9 ± 0.31	2.6 ± 0.516	1.4 ± 0.69	-	-
Fibrin glue	2 ± 0.66	2.1 ± 0.31 <sup>a</sup>	2.1 ± 0.31 <sup>a</sup>	2.1 ± 0.31 <sup>a</sup>	2 ± 0.47	2.6 ± 0.516	1.3 ± 0.67	-	-
<i>Buk et al</i> [35]									
Control	2.3 ± 0.82	1.9 ± 0.56 <sup>a</sup>	1.8 ± 0.42 <sup>a</sup>	2 ± 0.47	2.1 ± 0.56 <sup>a</sup>	2.6 ± 0.966	0.8 ± 0.63 <sup>a</sup>	-	-
Oxaliplatin	2.5 ± 0.52	2.9 ± 0.52 <sup>a</sup>	2.4 ± 0.51 <sup>a</sup>	2.5 ± 0.52	2.8 ± 0.42 <sup>a</sup>	2.6 ± 0.516	2 ± 0.94 <sup>a</sup>	-	-
Oxaliplatin + PRP	2.7 ± 0.58	2 ± 0.47 <sup>a</sup>	1.8 ± 0.42 <sup>a</sup>	2.3 ± 0.67	2.1 ± 0.56 <sup>a</sup>	2.5 ± 0.54	1.6 ± 0.96 <sup>a</sup>	-	-
<i>Aydin et al</i> [17]									
Control	1 ± 1	2 ± 1	-	2 ± 0	2 ± 1	3 ± 1	3 ± 0	-	-
L-PRP	0 ± 2	2 ± 1	-	2 ± 0	1 ± 0 <sup>a</sup>	2.5 ± 1 <sup>a</sup>	3 ± 2	-	-
H-PRP	1.5 ± 2	2 ± 2	-	2 ± 1	0 ± 0 <sup>a</sup>	1 ± 2 <sup>a</sup>	3 ± 0	-	-
<i>Göksu et al</i> [30]									
Control	2.38 ± 0.51	2.38 ± 0.518	2.38 ± 0.51 <sup>a</sup>	-	2.75 ± 0.46 <sup>a</sup>	2.63 ± 0.51	1.75 ± 0.46	-	-
5-FU	2.63 ± 0.51	2.50 ± 0.463	2.63 ± 0.51 <sup>a</sup>	-	2.75 ± 0.46 <sup>a</sup>	2.50 ± 0.53	1.25 ± 0.46	-	-
5-FU + PRP	2.13 ± 0.35	2.13 ± 0.518	2 ± 1 <sup>a</sup>	-	2 ± 0.53 <sup>a</sup>	2.63 ± 0.51	1.25 ± 0.46	-	-
<i>Sozutek et al</i> [31]									
Control	0.3 ± 0.48	1.3 ± 0.94	1 ± 0.47	1 ± 0 <sup>a</sup>	0.4 ± 0.51	0.3 ± 0.48	-	0.6 ± 0.51	4.9 ± 1.28
Control + PRP	0.2 ± 0.42	0.7 ± 0.67	1 ± 0.47	1.6 ± 0.51 <sup>a</sup>	0.3 ± 0.48	0.4 ± 0.48	-	0.2 ± 0.42	4.3 ± 1.33
Septic	1.1 ± 0.64	1.5 ± 0.53	1.6 ± 0.51 <sup>a</sup>	1.1 ± 0.83	1.2 ± 0.71 <sup>a</sup>	1 ± 0.53	-	1.2 ± 0.71	9.8 ± 1.12 <sup>a</sup>
Septic + PRP	0.7 ± 0.48	1.2 ± 0.42	1.3 ± 0.48 <sup>a</sup>	1.5 ± 0.52	0.4 ± 0.51 <sup>a</sup>	0.5 ± 0.51	-	0.8 ± 0.42	6.1 ± 1.37 <sup>a</sup>
<i>Gorur et al</i> [32]									
Control	0.3 ± 0.67 <sup>a</sup>	1.3 ± 0.9	1 ± 0.47	1 ± 0	1.1 ± 0.31 <sup>a</sup>	0.3 ± 0.57 <sup>a</sup>	-	1.2 ± 0.78 <sup>a</sup>	-
5-FU	1 ± 1.05 <sup>a</sup>	1.5 ± 0.53	1.4 ± 0.32	1.1 ± 0.83	2 ± 0.73 <sup>a</sup>	1.1 ± 0.42 <sup>a</sup>	-	1.5 ± 0.52 <sup>a</sup>	-
Control + PRP	0 <sup>a</sup>	0.7 ± 0.67	1 ± 0.67	1.8 ± 0.31	1 ± 0.47 <sup>a</sup>	0.3 ± 0.57 <sup>a</sup>	-	0.9 ± 0.87 <sup>a</sup>	-
5-FU + PRP	0.1 ± 0.3	1.2 ± 0.42	1.5 ± 0.58	1.6 ± 0.53	1.7 ± 0.48	0.6 ± 0.57	-	1.1 ± 0.31	-

<sup>a</sup>P < 0.05, represents a statistically significant difference between values.

5-FU: 5-Fluorouracil; PRP: Platelet rich plasma.

Aydin *et al*[17] reported that PRP coated sutures with either high or low platelet concentration resulted in significantly decreased formation of granulation tissue compared to the control group[17]. In contrast, Fresno *et al*[19] reported that on postoperative day 7 the PRP treated anastomosis developed increased, but not significantly different, mature granulation tissue and fibrosis. Yali *et al*[36] findings were significant for higher vascularization, fibroblast organization and epithelial formation in the PRP treated peritonitis model. Pehlivanli *et al*[33] compared several agents and concluded that PRP application was associated with better re-epithelialization scores compared to Zeolite application and control groups.

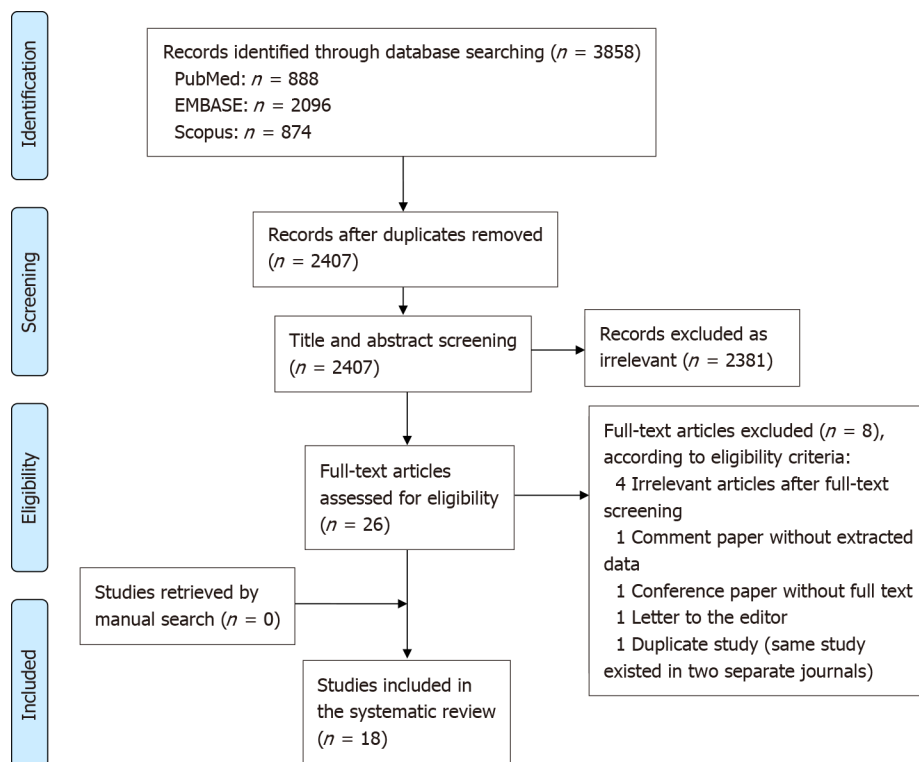


Figure 1 PRISMA flow diagram of the study selection process.

Giusto *et al*[28] reported no statistically significant changes in neovascularization and fibroblast proliferation. Mucosa epithelialization was significantly increased in the PRGF group. Yol *et al*[10] found that the fibroblast count was significantly increased in the PRP group compared to the control group, but the results were comparable between the PRP and the bioglue groups. In addition, Daglioglu *et al*[9] showed that fibroblast density and neovascularization were not significantly different between the fibrin glue or PRP application and control groups. Buk *et al*[35] reported that submucosal bridging was significantly increased in the control and PRP/oxaliplatin groups compared to the oxaliplatin group alone. Lastly, Zhou *et al*[29], utilizing an open abdomen animal model, reported that fibroblast ingrowth was significantly higher in the PRP group compared to the control and open abdomen group. The vascular ingrowth of the PRP was significantly increased compared to the open abdomen, but was comparable to the control group[29].

### Study quality and risk of bias

Regarding selection bias, 17 of the 18 included studies (94%) did not report whether the allocation sequence was adequately applied and concealed. Only one study reported the use of a random number generator. Concerning the baseline characteristics, 10 of the 18 studies (56%) described comparable groups at the baseline.

Regarding performance bias, one study reported that the researchers were blinded, while other studies did not report data regarding the housing parameters or researcher's blinding. Therefore, the risk of bias is considered unclear.

Regarding detection bias and specifically the animals' selection method for the assessment of outcomes, all studies were scored as having unclear risk of bias due to missing relevant information. However, outcome assessment methods were similar between the groups in all studies and the risk of bias regarding the blinding of the outcome assessors is characterized as low.

Regarding attrition bias, 5 of the 18 included studies (28%) did not describe the handling method for incomplete data (unclear bias). Two studies were scored as high risk of bias, including one study where the authors excluded unequal number of animals that died in different groups and another study where the authors did not provide sufficient information about the death of two animals in one of the groups.

Regarding reporting bias, in 17 of the 18 studies (94%) adequately described the outcomes and the reporting bias risk was low. In one study, the tissue hydroxyproline levels were not reported, despite being included as an expected outcome in the materials and method section (high risk).

Regarding other sources of bias, in one study a preparation kit was used and one of the co-authors had a relevant conflict of interest with the manufacturer. Two studies (11%) did not provide information regarding any funding that may have affected their work.

Regarding the approval from an ethical committee, all included studies reported approval from their local ethical committee. The quality assessment results are summarized in [Supplementary Table 2](#).

## DISCUSSION

The application of PRP in bowel anastomosis is associated with improved outcomes in terms of anastomoses bursting pressure and tissue hydroxyproline, which are the two most common parameters used for the evaluation of anastomosis integrity[17].

Anastomotic bursting pressure is an indirect indicator of anastomosis healing. It reflects the balance between collagen synthesis and degradation[18,38]. Although 50% (9/18) of the included studies reported no statistically significant changes in the anastomosis bursting pressure in PRP-treated compared to control groups, five studies reported that the application of PRP in the presence of an underlying medical or surgical condition, improved the anastomosis bursting pressure. Furthermore, the application of PRP in the open abdomen, ischemic / reperfusion injury, peritonitis, intraperitoneal 5-fluorouracil (5-FU) infusion, and hyperthermic intraperitoneal chemotherapy with 5-FU animal models was associated with statistically significant improved anastomosis bursting pressure[16,29,30,32,36]. Among, the other four studies, Dauser *et al*[26] investigated the application of PRF, which presents some component differences compared to PRP. Giusto *et al*[28] reported significantly lower bursting pressure in the PRP compared to the control group, although the application of PRGF significantly increased the anastomotic bursting pressure compared to PRP or control group. Lastly, Daradka *et al*[27] used PRP coated sutures and Pehlivanli *et al* [33] studied the application of several topical factors in the anastomosis. Both studies report no significant changes in anastomotic bursting pressure in PRP compared to control groups.

Hydroxyproline level is a widely accepted marker of tissue collagen synthesis, including the anastomotic area[39]. Increased collagen synthesis and collagen maturation are thought to be induced by hydroxyproline molecules[10]. Low levels of tissue hydroxyproline exert a negative impact in wound healing[40,41]. According to the included studies, tissue hydroxyproline is measured on or close to the 7<sup>th</sup> postoperative day. Despite not being reported by six studies, tissue hydroxyproline levels were consistent with the anastomotic bursting pressure in all except three studies. In two studies the anastomotic bursting pressure was significantly increased in the PRP-treated group while anastomotic tissue hydroxyproline levels did not show any significant changes[17,34]. Gorur *et al*[32] reported that PRP application was associated with increased tissue hydroxyproline levels in the intraperitoneal 5-FU infusion animal model.

Similarly, anastomotic wound inflammatory cellular infiltration in control compared to PRP groups did not show any statistically significant changes among the included studies. However, it was reported that in the presence of an underlying detrimental condition like intraperitoneal chemotherapy or infection, PRP application significantly decreased the inflammatory cellular infiltration in bowel anastomosis[30-32,34-36]. Theoretically, enhanced anastomosis strength associated with PRP application could partially be attributed to decreased inflammatory cell-mediated collagen degradation[42].

The intestinal wound healing process can be roughly divided into three phases: inflammation, proliferation, and maturation. Following a surgical intervention, platelets are among the first cells that reach the traumatized tissue area, while their main functions include the formation of a protective clot and the release of growth factors[43]. The role of growth factors in wound healing has been extensively investigated in previous studies. PDGF secretion was shown to improve epithelialization, secretion of several other tissue growth factors, and tissue regeneration[44]. Synthesis and deposition of several extracellular matrix factors as well as increased *in vitro* keratinocyte motility have been associated with FGF[45]. VEGF family proteins play a significant role in early angiogenesis. *In vitro* studies have demonstrated that the VEGF family proteins facilitate the angiogenic properties of stem cells and improve the wound healing process[46,47]. IGF acts as a mitogenic growth factor for fibroblasts [48]. PRP, which is a carrier of growth factors, is expected to improve the anastomosis

wound healing and reduce the incidence of postoperative anastomosis-related complications (Figure 2).

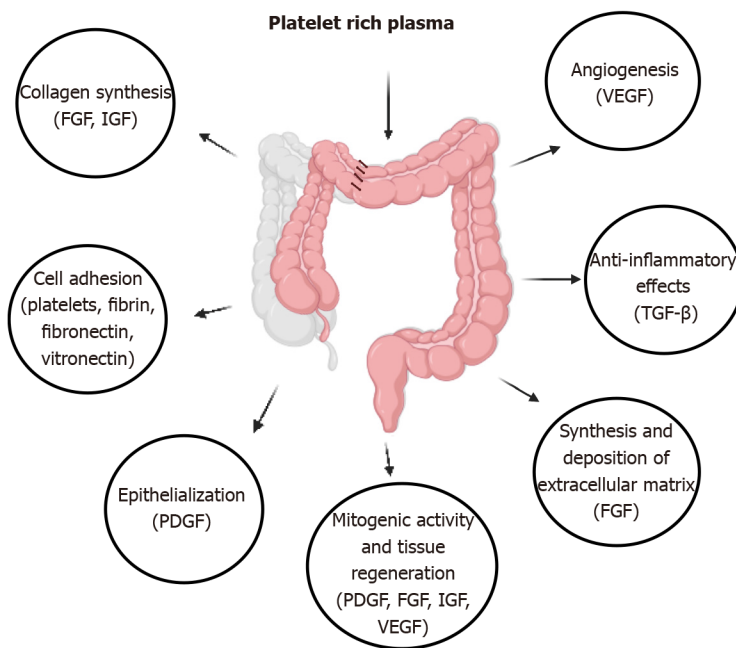
The first week following a bowel anastomosis seems to be the critical period for the development of anastomosis leaks. Most of the anastomosis leakages are reported 5-10 d postoperatively, when the strength of anastomosis is considered to be at its lowest level[49]. A possible explanation involves the collagen remodeling during wound healing process. Experimental studies have shown that collagen degradation starts on the third postoperative day and peaks on the seventh day following surgical trauma. Permanent collagen deposition in the anastomotic area is believed to take place a few days postoperatively. In view of initial collagen degradation during wound healing over the first few days, the anastomosis integrity is mainly supported by fibrin deposition and anastomotic technique (suturing method)[9,29,35,50,51]. Based on these experimental studies, all included studies investigated the effects of PRP application around postoperative day 7, when the anastomotic strength is considered to be at its lowest level.

Anastomotic leak is associated with increased morbidity and mortality rate[10,52]. Dysregulation of circulating platelets, the main component of PRP, has been associated with anastomotic leak. Both thrombocytosis and thrombocytopenia have been described as factors associated with anastomotic leak. However, these results should be interpreted with caution as the dysregulation of circulating platelets could be attributed to malnutrition (thrombocytopenia) or sepsis (thrombocytosis), which are well established risk factors associated with anastomotic leak[53,54]. Patients developing anastomotic leaks tend to have prolonged intensive care unit and hospital stay and significantly increased medical care costs[29]. Intra-abdominal infections, fistulas between adjacent organs, and poor abdominal wound healing are some of the long-term complications of anastomotic leak that may result in significant consequences on patient's quality of life[55].

The optimal method and/or agent to prevent these detrimental complications has not been identified yet. The prevention of bowel anastomosis leak involves the modification of risk factors that predispose to impaired wound healing. To this end, immunomodulators, hormones, growth factors, antibiotics and proteinase inhibitors have been previously applied topically or administered systemically and have been associated with improved bowel anastomotic healing[56]. The underlying mechanisms that promote enhanced anastomosis integrity, include increased blood supply, reduced inflammatory cell infiltration, and rapid collagen deposition[56]. Despite the presence of numerous studies on agents that could promote wound healing, the ideal agent is yet to be determined. PRP contains a variety of growth factors, immunomodulators, as well as other constituents that promote tissue healing and is a promising candidate in terms of clinical applications.

Preparation of PRP is a simple process with very low cost compared to other materials used for anastomosis reinforcement[57]. Currently, most studies report that a sample of 5-20 mL of peripheral blood is required to extract 2-5 mL of PRP. The amount of peripheral blood required for PRP preparation depends on the technique or commercial kit that are used during the isolation process[14,58]. Furthermore, its autologous nature increases biocompatibility[9,32]. However, some technical issues and concerns were raised among the included studies. The majority of the growth factors are presynthesized within the platelets and are secreted within one hour after platelet activation. As a result PRP associated growth factors are released immediately after PRP application to the anastomotic area[19,59]. Interestingly, platelets could also synthesize and secrete growth factors during their lifespan in the area of bowel anastomosis for up to 7 d. This growth factor release is supplemental to the initial growth factor secretion taking place immediately after PRP application[10,19,60]. Nevertheless, the platelet concentration of PRP applied to the anastomotic area may also affect the healing outcomes. To that extend, Aydin *et al*[17] showed that low platelet concentration results in superior outcomes in terms of anastomotic bursting pressure and collagen concentration at the anastomotic site compared to high platelet concentration PRP.

Our study has several strengths, including the total number of included studies, the large number of animal models, as well the variety of conditions that the PRP was tested on. However, we have to recognize that our findings are not free of limitations and should be interpreted cautiously. Animal models, studies heterogeneity and small samples are among the major limitations of our study. Only two studies investigated the effects of PRP on pigs, which have intestines that are structurally closer to human bowel. As a result, the clinical application and generalizability of our findings in large animal models are questionable. Furthermore, high heterogeneity was observed in the histopathological scales used for the assessment of anastomotic cellular infiltration.



**Figure 2 Platelet rich plasma effect on the healing process of bowel anastomosis (created with BioRender.com).** FGF: Fibroblast growth factor; IGF: Insulin-like growth factor; PDGF: Platelet-derived growth factor; TGF- $\beta$ : Transforming growth factor- $\beta$ ; VEGF: Vascular endothelial growth factor.

Although pathologists were reported to be blinded regarding the origin of the samples, the lack of a uniform scale, such as the Verhofstad scale, pose difficulties in terms of results interpretation and measurement bias.

## CONCLUSION

The application of PRP in bowel anastomosis is a feasible approach and it seems to improve the integrity of bowel anastomosis. PRP application compared to control groups did not show any significant changes in the majority of the included studies. However, in the presence of an underlying condition that impairs intestinal wound healing, including peritonitis or chemotherapy, the application of PRP could potentially improve the healing process. Its preparation does not require significant expertise and can be easily extracted from patient's own blood. Taking into consideration its cost effectiveness, PRP could be considered in the clinical practice for bowel anastomosis reinforcement material. Apparently, further research is needed to confirm the safety and effectiveness of PRP on human bowel anastomoses.

## ARTICLE HIGHLIGHTS

### Research background

Several applications of platelet rich plasma (PRP) have been reported in the literature. Some examples include maxillofacial, orthopedic and plastic surgery where PRP is considered to improve the wound healing process. PRP is easily extracted from patient's blood and includes a variety of growth factor that is thought to improve the wound healing process.

### Research motivation

Preclinical studies shows that the PRP has a positive impact in the healing process of bowel anastomosis.

### Research objectives

The aim of this study is to define the role of PRP in general surgery, especially in procedures involving bowel anastomosis. Therefore, a systematic review of the literature was performed.



- 1 **Midura EF**, Hanseman D, Davis BR, Atkinson SJ, Abbott DE, Shah SA, Paquette IM. Risk factors and consequences of anastomotic leak after colectomy: a national analysis. *Dis Colon Rectum* 2015; **58**: 333-338 [PMID: [25664712](#) DOI: [10.1097/DCR.0000000000000249](#)]
- 2 **Murray AC**, Chiuzan C, Kiran RP. Risk of anastomotic leak after laparoscopic vs open colectomy. *Surg Endosc* 2016; **30**: 5275-5282 [PMID: [27126618](#) DOI: [10.1007/s00464-016-4875-0](#)]
- 3 **Walker KG**, Bell SW, Rickard MJ, Mehanna D, Dent OF, Chapuis PH, Bokey EL. Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. *Ann Surg* 2004; **240**: 255-259 [PMID: [15273549](#) DOI: [10.1097/01.sla.0000133186.81222.08](#)]
- 4 **Law WL**, Choi HK, Lee YM, Ho JW, Seto CL. Anastomotic leakage is associated with poor long-term outcome in patients after curative colorectal resection for malignancy. *J Gastrointest Surg* 2007; **11**: 8-15 [PMID: [17390180](#) DOI: [10.1007/s11605-006-0049-z](#)]
- 5 **Hompes D**, D'Hoore A, Van Cutsem E, Fieuw S, Ceelen W, Peeters M, Van der Speeten K, Bertrand C, Legendre H, Kerger J. The treatment of peritoneal carcinomatosis of colorectal cancer with complete cytoreductive surgery and hyperthermic intraperitoneal peroperative chemotherapy (HIPEC) with oxaliplatin: a Belgian multicentre prospective phase II clinical study. *Ann Surg Oncol* 2012; **19**: 2186-2194 [PMID: [22395983](#) DOI: [10.1245/s10434-012-2264-z](#)]
- 6 **Riss S**, Chandrakumaran K, Dayal S, Cecil TD, Mohamed F, Moran BJ. Risk of definitive stoma after surgery for peritoneal malignancy in 958 patients: comparative study between complete cytoreductive surgery and maximal tumor debulking. *Eur J Surg Oncol* 2015; **41**: 392-395 [PMID: [25238953](#) DOI: [10.1016/j.ejso.2014.09.002](#)]
- 7 **Whealon MD**, Gahagan JV, Sujatha-Bhaskar S, O'Leary MP, Selleck M, Dumitra S, Lee B, Senthil M, Pigazzi A. Is Fecal Diversion Needed in Pelvic Anastomoses During Hyperthermic Intraperitoneal Chemotherapy (HIPEC)? *Ann Surg Oncol* 2017; **24**: 2122-2128 [PMID: [28411306](#) DOI: [10.1245/s10434-017-5853-z](#)]
- 8 **Kingham TP**, Pachter HL. Colonic anastomotic leak: risk factors, diagnosis, and treatment. *J Am Coll Surg* 2009; **208**: 269-278 [PMID: [19228539](#) DOI: [10.1016/j.jamcollsurg.2008.10.015](#)]
- 9 **Daglioglu YK**, Duzgun O, Sarici IS, Ulutas KT. Comparison of platelet rich plasma vs fibrin glue on colonic anastomoses in rats. *Acta Cir Bras* 2018; **33**: 333-340 [PMID: [29768536](#) DOI: [10.1590/s0006-70822018000000000000000000000](#)]

- 10.1590/s0102-865020180040000005]
- 10 **Yol S**, Tekin A, Yilmaz H, Küçükartallar T, Esen H, Caglayan O, Tatkan Y. Effects of platelet rich plasma on colonic anastomosis. *J Surg Res* 2008; **146**: 190-194 [PMID: [18028949](#) DOI: [10.1016/j.jss.2007.05.015](#)]
  - 11 **Saleem M**, Pisani F, Zahid FM, Georgakopoulos I, Pustina-Krasniqi T, Xhajanka E, Almasri M. Adjunctive Platelet-Rich Plasma (PRP) in Infrabony Regenerative Treatment: A Systematic Review and RCT's Meta-Analysis. *Stem Cells Int* 2018; **2018**: 9594235 [PMID: [29755531](#) DOI: [10.1155/2018/9594235](#)]
  - 12 **Alio JL**, Rodriguez AE, De Arriba P, Gisbert S, Abdelghany AA. Treatment with platelet-rich plasma of surgically related dormant corneal ulcers. *Eur J Ophthalmol* 2018; **28**: 515-520 [PMID: [29566537](#) DOI: [10.1177/1120672117747042](#)]
  - 13 **Huang Y**, Liu X, Xu X, Liu J. Intra-articular injections of platelet-rich plasma, hyaluronic acid or corticosteroids for knee osteoarthritis : A prospective randomized controlled study. *Orthopade* 2019; **48**: 239-247 [PMID: [30623236](#) DOI: [10.1007/s00132-018-03659-5](#)]
  - 14 **Hamid MSA**. Cost Effectiveness of a Platelet-rich Plasma Preparation Technique for Clinical Use. *Wounds* 2018; **30**: 186-190 [PMID: [30059343](#)]
  - 15 **Estcourt LJ**, Malouf R, Hopewell S, Trivella M, Doree C, Stanworth SJ, Murphy MF. Pathogen-reduced platelets for the prevention of bleeding. *Cochrane Database Syst Rev* 2017; **7**: CD009072 [PMID: [28756627](#) DOI: [10.1002/14651858.CD009072.pub3](#)]
  - 16 **Özçay N**, Özdemir H, Besim H. Role of platelet-rich fibrin on intestinal anastomosis wound healing in a rat. *Biomed Mater* 2018; **13**: 045006 [PMID: [29565259](#) DOI: [10.1088/1748-605X/aab8e1](#)]
  - 17 **Aydin MA**, Guler EM, Demiroz AS, Aydin MF, Saglam G. Comparison of Platelet-Rich Plasma-Impregnated Suture Material with Low and High Platelet Concentration to Improve Colonic Anastomotic Wound Healing in Rats. *Gastroenterol Res Pract* 2020; **2020**: 7386285 [PMID: [32565785](#) DOI: [10.1155/2020/7386285](#)]
  - 18 **Yamaguchi R**, Terashima H, Yoneyama S, Tadano S, Ohkohchi N. Effects of platelet-rich plasma on intestinal anastomotic healing in rats: PRP concentration is a key factor. *J Surg Res* 2012; **173**: 258-266 [PMID: [21074782](#) DOI: [10.1016/j.jss.2010.10.001](#)]
  - 19 **Fresno L**, Fondevila D, Bambo O, Chacaltana A, García F, Andaluz A. Effects of platelet-rich plasma on intestinal wound healing in pigs. *Vet J* 2010; **185**: 322-327 [PMID: [19616459](#) DOI: [10.1016/j.tvjl.2009.06.009](#)]
  - 20 **Liberati A**, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700 [PMID: [19622552](#) DOI: [10.1136/bmj.b2700](#)]
  - 21 **Wohlin C**. Guidelines for Snowballing in Systematic Literature Studies and a Replication in Software Engineering. Proceedings of the 18th International Conference on Evaluation and Assessment in Software Engineering (EASE '14); 2014 May. New York, NY, USA: Association for Computing Machinery, 2014: 1-10 [DOI: [10.1145/2601248.2601268](#)]
  - 22 **Hooijmans CR**, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Methodol* 2014; **14**: 43 [PMID: [24667063](#) DOI: [10.1186/1471-2288-14-43](#)]
  - 23 **Covidence**. Covidence systematic review software, Veritas Health Innovation, Melbourne AA. [cited 10 March 2021]. In: Covidence [Internet]. Available from: [www.covidence.org](http://www.covidence.org)
  - 24 **Dzhumabekov BN**, Dzhumabekov AT, Ismailov DK, Baitileuov TA, Fakhradyiev IR. Platelet-rich autoplasm effect on intestinal anastomosis regeneration in rabbits. *Arch Balk Med Union* 2019; **54**: 621-629 [DOI: [10.31688/ABMU.2019.54.4.02](#)]
  - 25 **Dzhumabekov BN**, Dzhumabekov AT, Ismailov DK, Baitileuov TA, Fakhradyiev IR. Platelet-rich autoplasm effect on intestinal anastomosis regeneration in rabbits. *Libr Oncol* 2019; **47**: 55-63 [DOI: [10.20471/LO.2019.47.02-03.11](#)]
  - 26 **Dauser B**, Heitland W, Bader FG, Brunner W, Nir Y, Zbar AP. Histologic changes in early colonic anastomotic healing using autologous platelet-rich fibrin matrix. *Eur Surg - Acta Chir Austriaca* 2020; **52**: 155-164 [DOI: [10.1007/s10353-019-0578-9](#)]
  - 27 **Daradka M**, Alardah MM, Ismail ZB. Effects of autologous platelet-rich plasma coated sutures on intestinal anastomotic healing in rabbits. *Heliyon* 2019; **5**: e02713 [PMID: [31840125](#) DOI: [10.1016/j.heliyon.2019.e02713](#)]
  - 28 **Giusto G**, Vercelli C, Iussich S, Tursi M, Perona G, Gandini M. Comparison of the effects of platelet-rich or growth factor-rich plasma on intestinal anastomosis healing in pigs. *BMC Vet Res* 2017; **13**: 188 [PMID: [28629420](#) DOI: [10.1186/s12917-017-1102-8](#)]
  - 29 **Zhou B**, Ren J, Ding C, Wu Y, Chen J, Wang G, Gu G, Li J. Protection of colonic anastomosis with platelet-rich plasma gel in the open abdomen. *Injury* 2014; **45**: 864-868 [PMID: [24552769](#) DOI: [10.1016/j.injury.2014.01.018](#)]
  - 30 **Göksu M**, Alakuş H, Ertan S, Akgün S. Effect of platelet-rich plasma on colon anastomosis in rats in which hyperthermic intra-peritoneal chemotherapy was performed using 5-fluorouracil. *ANZ J Surg* 2020; **90**: 2290-2297 [PMID: [32436284](#) DOI: [10.1111/ans.15993](#)]
  - 31 **Sozutek A**, Colak T, Cetinkunar S, Reyhan E, Irkorucu O, Polat G, Cennet A. The Effect of Platelet-Rich-Plasma on the Healing of Left Colonic Anastomosis in a Rat Model of Intra-Abdominal Sepsis. *J Invest Surg* 2016; **29**: 294-301 [PMID: [26822265](#) DOI: [10.3109/08941939.2015.1111473](#)]
  - 32 **Gorur M**, Sozutek A, Irkorucu O, Karakaya B. The influence of platelet-rich plasma (PRP) on

- colonic anastomosis healing impaired by intraperitoneal 5-fluorouracil application. An experimental study. *Acta Cir Bras* 2020; **35**: e202000504 [PMID: [32638844](#) DOI: [10.1590/s0102-8650202000500000004](#)]
- 33 **Pehlivanli F**, Karaca G, Aydin O, Altunkaya C, Şahiner İt, Özden H, Hafize U, Pekicici Mr. Effects of thymoquinone, zeolite and platelet rich plasma on the healing of ischemic colonic anastomosis. *Kırıkkale Üniversitesi Tıp Fakültesi Derg* 2019; **21**: 65-72 [DOI: [10.24938/kutfd.522809](#)]
- 34 **Ocak S**, Buk OF, Genc B, Avcı B, Uzuner HO, Gundogdu SB. The effects of platelet-rich-plasma gel application to the colonic anastomosis in hyperthermic intraperitoneal chemotherapy: An experimental rat model. *Int Wound J* 2019; **16**: 1426-1432 [PMID: [31448554](#) DOI: [10.1111/iwj.13207](#)]
- 35 **Buk OF**, Ocak S, Genc B, Avcı B, Uzuner HO. Is platelet-rich plasma improves the anastomotic healing in hyperthermic intraperitoneal chemotherapy with oxaliplatin: an experimental rat study. *Ann Surg Treat Res* 2020; **98**: 89-95 [PMID: [32051817](#) DOI: [10.4174/ast.2020.98.2.89](#)]
- 36 **Yah AC**, Karagöz Eren S, Ertan T, Topuz Ö. Application of Platelet Rich Plasma in Experimental Colonic Anastomosis for Improved Strength. *Indian J Surg* 2020; **83**: 500-504 [DOI: [10.1007/s12262-020-02400-x](#)]
- 37 **Verhofstad MH**, Lange WP, van der Laak JA, Verhofstad AA, Hendriks T. Microscopic analysis of anastomotic healing in the intestine of normal and diabetic rats. *Dis Colon Rectum* 2001; **44**: 423-431 [PMID: [11289291](#) DOI: [10.1007/BF02234744](#)]
- 38 **Kerem M**, Bedirli A, Karahacioglu E, Pasaoglu H, Sahin O, Bayraktar N, Yilmaz TU, Sakrak O, Goksel F, Oguz M. Effects of soluble fiber on matrix metalloproteinase-2 activity and healing of colon anastomosis in rats given radiotherapy. *Clin Nutr* 2006; **25**: 661-670 [PMID: [16677740](#) DOI: [10.1016/j.clnu.2006.01.028](#)]
- 39 **Munireddy S**, Kavalukas SL, Barbul A. Intra-abdominal healing: gastrointestinal tract and adhesions. *Surg Clin North Am* 2010; **90**: 1227-1236 [PMID: [21074038](#) DOI: [10.1016/j.suc.2010.08.002](#)]
- 40 **Srivastava AK**, Khare P, Nagar HK, Raghuvanshi N, Srivastava R. Hydroxyproline: A Potential Biochemical Marker and Its Role in the Pathogenesis of Different Diseases. *Curr Protein Pept Sci* 2016; **17**: 596-602 [PMID: [26916157](#) DOI: [10.2174/1389203717666151201192247](#)]
- 41 **Bucknall TE**. The effect of local infection upon wound healing: an experimental study. *Br J Surg* 1980; **67**: 851-855 [PMID: [6160895](#) DOI: [10.1002/bjs.1800671205](#)]
- 42 **Newton PM**, Watson JA, Wolowacz RG, Wood EJ. Macrophages restrain contraction of an *in vitro* wound healing model. *Inflammation* 2004; **28**: 207-214 [PMID: [15673162](#) DOI: [10.1023/B:IFLA.0000049045.41784.59](#)]
- 43 **Witte MB**, Barbul A. General principles of wound healing. *Surg Clin North Am* 1997; **77**: 509-528 [PMID: [9194878](#) DOI: [10.1016/s0039-6109\(05\)70566-1](#)]
- 44 **Mio T**, Adachi Y, Romberger DJ, Ertl RF, Rennard SI. Regulation of fibroblast proliferation in three-dimensional collagen gel matrix. *In Vitro Cell Dev Biol Anim* 1996; **32**: 427-433 [PMID: [8856343](#) DOI: [10.1007/BF02723005](#)]
- 45 **Lee SH**, Lee JH, Cho KH. Effects of Human Adipose-derived Stem Cells on Cutaneous Wound Healing in Nude Mice. *Ann Dermatol* 2011; **23**: 150-155 [PMID: [21747612](#) DOI: [10.5021/ad.2011.23.2.150](#)]
- 46 **Huang SP**, Hsu CC, Chang SC, Wang CH, Deng SC, Dai NT, Chen TM, Chan JY, Chen SG, Huang SM. Adipose-derived stem cells seeded on acellular dermal matrix grafts enhance wound healing in a murine model of a full-thickness defect. *Ann Plast Surg* 2012; **69**: 656-662 [PMID: [23154338](#) DOI: [10.1097/SAP.0b013e318273f909](#)]
- 47 **Song SH**, Lee MO, Lee JS, Jeong HC, Kim HG, Kim WS, Hur M, Cha HJ. Genetic modification of human adipose-derived stem cells for promoting wound healing. *J Dermatol Sci* 2012; **66**: 98-107 [PMID: [22472356](#) DOI: [10.1016/j.jdermsci.2012.02.010](#)]
- 48 **Mason RM**, Wahab NA. Extracellular matrix metabolism in diabetic nephropathy. *J Am Soc Nephrol* 2003; **14**: 1358-1373 [PMID: [12707406](#) DOI: [10.1097/01.asn.0000065640.77499.d7](#)]
- 49 **Li YW**, Lian P, Huang B, Zheng HT, Wang MH, Gu WL, Li XX, Xu Y, Cai SJ. Very Early Colorectal Anastomotic Leakage within 5 Post-operative Days: a More Severe Subtype Needs Relaparatomy. *Sci Rep* 2017; **7**: 39936 [PMID: [28084305](#) DOI: [10.1038/srep39936](#)]
- 50 **Hyman N**, Manchester TL, Osler T, Burns B, Cataldo PA. Anastomotic leaks after intestinal anastomosis: it's later than you think. *Ann Surg* 2007; **245**: 254-258 [PMID: [17245179](#) DOI: [10.1097/01.sla.0000225083.27182.85](#)]
- 51 **Schiff A**, Roy S, Pignot M, Ghosh SK, Fegelman EJ. Diagnosis and Management of Intraoperative Colorectal Anastomotic Leaks: A Global Retrospective Patient Chart Review Study. *Surg Res Pract* 2017; **2017**: 3852731 [PMID: [28695192](#) DOI: [10.1155/2017/3852731](#)]
- 52 **Gessler B**, Eriksson O, Angenete E. Diagnosis, treatment, and consequences of anastomotic leakage in colorectal surgery. *Int J Colorectal Dis* 2017; **32**: 549-556 [PMID: [28070659](#) DOI: [10.1007/s00384-016-2744-x](#)]
- 53 **Yeap E**, Teoh WMK, Nguyen TC, Suhardja TS. Preoperative anaemia and thrombocytopenia are associated with venous thromboembolism complications after colorectal resection. *ANZ J Surg* 2021; **91**: E32-E37 [PMID: [32356410](#) DOI: [10.1111/ans.15918](#)]
- 54 **Nikolian VC**, Kamdar NS, Regenbogen SE, Morris AM, Byrn JC, Suwanabol PA, Campbell DA Jr, Hendren S. Anastomotic leak after colorectal resection: A population-based study of risk factors and hospital variation. *Surgery* 2017; **161**: 1619-1627 [PMID: [28238345](#) DOI: [10.1016/j.surg.2016.12.033](#)]

- 55 **Vertrees A**, Wakefield M, Pickett C, Greer L, Wilson A, Gillern S, Nelson J, Aydelotte J, Stojadinovic A, Shriver C. Outcomes of primary repair and primary anastomosis in war-related colon injuries. *J Trauma* 2009; **66**: 1286-91; discussion 1291 [PMID: [19430228](#) DOI: [10.1097/TA.0b013e31819ea3fc](#)]
- 56 **Oines MN**, Krarup PM, Jorgensen LN, Agren MS. Pharmacological interventions for improved colonic anastomotic healing: a meta-analysis. *World J Gastroenterol* 2014; **20**: 12637-12648 [PMID: [25253969](#) DOI: [10.3748/wjg.v20.i35.12637](#)]
- 57 **Casella G**, Soricelli E, Genco A, Ferrazza G, Basso N, Redler A. Use of platelet-rich plasma to reinforce the staple line during laparoscopic sleeve gastrectomy: feasibility study and preliminary outcome. *J Laparoendosc Adv Surg Tech A* 2015; **25**: 222-227 [PMID: [25668681](#) DOI: [10.1089/lap.2014.0329](#)]
- 58 **Samadi P**, Sheykhasan M, Khoshinani HM. The Use of Platelet-Rich Plasma in Aesthetic and Regenerative Medicine: A Comprehensive Review. *Aesthetic Plast Surg* 2019; **43**: 803-814 [PMID: [30552470](#) DOI: [10.1007/s00266-018-1293-9](#)]
- 59 **Marx RE**. Platelet-rich plasma: evidence to support its use. *J Oral Maxillofac Surg* 2004; **62**: 489-496 [PMID: [15085519](#) DOI: [10.1016/j.joms.2003.12.003](#)]
- 60 **Marx RE**. Platelet-rich plasma (PRP): what is PRP and what is not PRP? *Implant Dent* 2001; **10**: 225-228 [PMID: [11813662](#) DOI: [10.1097/00008505-200110000-00002](#)]



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