Systematic Review

Probiotics Evaluation in Oncological Surgery: A Systematic Review of 36 Randomized Controlled Trials Assessing 21 Diverse Formulations

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Abstract: Background: Objectives were to evaluate probiotics safety and efficacy in oncological surgery. Methods: Systematic review methodology guided by Cochrane, PRISMA, SWiM, and CIOMS. Protocol registered on PROSPERO (CRD42018086168). Results: 36 RCTs (on 3305 participants) and 6 nonrandomized/observational studies were included, mainly on digestive system cancers. There was evidence of a beneficial effect on preventing infections, with 70% of RCTs’ (21/30) direction of effect favoring probiotics. However, five RCTs (17%) favored controls for infections, including one trial with RR 1.57 (95% CI: 0.79, 3.12). One RCT that changed (balanced) its antibiotics protocol after enrolling some participants had mortality risk RR 3.55 (95% CI: 0.77, 16.47; 7/64 vs. 2/65 deaths). The RCT identified with the most promising results overall administered an oral formulation of Lactobacillus acidophilus LA-5 + Lactobacillus plantarum + Bifidobacterium lactis BB-12 + Saccharomyces boulardii. Methodological quality appraisals revealed an overall substantial risk-of-bias, with only five RCTs judged as low risk-of-bias. Conclusions: This large evidence synthesis found encouraging results from most formulations, though this was contrasted by potential harms from a few others, thus validating the literature that “probiotics” are not homogeneous microorganisms. Given microbiome developments and infections morbidity, further high-quality research is warranted using those promising probiotics identified herein.

Keywords: cancer; perioperative; symbiotics; probiotics; Lactobacillus; Bifidobacterium; nutritional supplements; microbiome; integrative; naturopath

1. Introduction

The research conducted by the Human Microbiome Project over the past decade, in addition to more recent collective initiatives, estimates that adults host between 1 and 10 times as many bacterial cells as human cells, with most residing in the colon [1]. The intestinal microbiota landscape is a complex ecosystem that is a fundamental biological component and prominently influences human health [2]. The interaction between gastrointestinal microorganisms and the host are complex, forming symbiotic relationships that can both support homeostasis [3], or promote disease development via fortuitous physiologic pathway dysregulation [4]. The microbiome can exert both pro- and anti-inflammatory responses, which may be related to immune functioning, as the immune
system can shape the composition of the microbiota [5]. Furthermore, studies have observed that intestinal bacteria may influence oncogenesis, tumor progression, and response to therapy [6]. Postoperative infections are an important factor affecting patient morbidity despite the application of prophylactic therapy with antibiotics and advanced surgical techniques [7]. The rate of developing postoperative infections among patients undergoing abdominal surgery has been estimated to be up to 30%, leading to a significant prolongation of hospital stay, and affecting quality of life [8]. Perioperative management, including antibiotic administration and mechanical bowel preparation, compounded by the physical trauma of surgery can alter the intestinal microbial landscape, intestinal mucosal barrier permeability, and intestinal immune functions [7].

According to a Joint FAO/WHO consensus, probiotics are defined as “live microorganisms which when administered in adequate amounts confer a health benefit on the host” [9]. Modifying the gut microbiota through the use of probiotics has been reported to positively affect various disease states, even in the absence of microbiome alterations. The proposed effects of probiotics and bacteria-colonizing foods may relate to their ability to share genes and metabolites, support challenged microbiota, and directly influence the epithelial and immune cells through modulation of a variety of pathways [10]. In vitro and in vivo studies have demonstrated several different inherent properties of probiotics, including anti-inflammatory, anti-proliferative, and antagonist effects against pathogens [11]. Symbiotics are products that combine probiotics with prebiotics, a specific subset of dietary fibers that are “selectively utilized by host microorganisms conferring a health benefit”, to exert synergistic effect [12]. Symbiotics may reduce pathogenic microorganisms by stimulating the growth of the commensal microbiota and subsequently increasing the production of short chain fatty acids, which are known to stabilize the intestinal barrier and local immune system [13]. Both Lactobacilli (L.) and Bifidobacteria (B.) are lactic acid-producing bacteria that can provide significant health benefits through improving food conversion, growth performance, modulating immune responses and intestinal crypt dynamics, and ultimately protecting against pathogens [14]. Previous systematic reviews in various surgical contexts have found encouraging results from probiotics at reducing postoperative infections and other complications [15]. However, knowledge is accumulating that these effects are likely strain specific [16]. Therefore, even though the literature often categorizes them together, not all probiotic supplements have equivalent safety or efficacy profiles due to their unique properties and effects [17].

While research has shown that the use of probiotics in the general population is generally safe and well tolerated, their application in vulnerable subpopulations requires further consideration of various factors along with careful probiotics selection [18]. The World Gastroenterology Organisation advises that “Most probiotics are designed for the generally healthy population, so use in persons with compromised immune function or underlying severe disease is best restricted to the strains and indications with proven efficacy” [19,20]. Furthermore, patients who are critically ill, hospitalized, immunocompromised, or on broad-spectrum antimicrobials are most at-risk for potentially developing rare adverse effects from probiotics, such as sepsis, fungemia, and gastrointestinal ischemia [21,22].

The complexity and wide array of this heterogeneous and inconsistent literature suggests a need to synthesize and critically appraise the human controlled evidence, with a special focus on evaluating the species and strains studied in diverse formulations. Our objectives were to evaluate the safety and efficacy of adjunctive probiotics use in oncological surgery by conducting an up-to-date, broad, and comprehensive evidence synthesis using rigorous systematic review methodology.
2. Materials and Methods

The complete methodology has been described in detail elsewhere [23]. Briefly, the protocol was registered a priori on PROSPERO (CRD42018086168), and followed guidance of the Cochrane Handbook [24], CIOMS Working Group X report [25], and PRISMA reporting criteria [26]. This publication is part of a larger endeavor to prepare multiple systematic reviews based on a prioritization exercise [27], to refine our research agenda and considering 10 natural health products. A detailed report covering the perioperative use of branched-chain amino acids stream was recently published [23]. Study inclusion criteria: studies evaluating synbiotics (i.e., probiotics with prebiotics) or probiotics in patients undergoing cancer-related surgery, any route of administration, duration, dose, and formulation (i.e., used alone or in combinations), compared to active control, placebo, or no added treatment (e.g., standard care). Primary review outcomes included hard endpoints of cancer therapy: cancer treatment response, metastasis/disease progression, mortality, recurrence, remission, and stable disease. Secondary outcomes: anthropometrics (e.g., body weight), bleeding, cancer biomarkers, immune cells, inflammatory marker levels, hospital length of stay, postoperative infections and antibiotics use, other postoperative complications (i.e., ileus/intestinal obstruction/constipation, diarrhea, nausea and vomiting), pain, quality of life, fatigue, and adverse events. Study designs for evaluation of efficacy were limited to randomized controlled trials (RCTs), while for the safety evaluation a broader evidence base was included of controlled observational cohort and case-control studies, nonrandomized and quasi-randomized controlled clinical trials, and RCTs. Studies with postoperative chemotherapy or radiation, non-English reports, and those not reporting probiotic nomenclature were excluded.

The following databases were searched from inception to September 19, 2020: MEDLINE, Embase, and Cochrane CENTRAL. The search strategy was peer reviewed by an expert medical librarian (JM) using the Peer Review of Electronic Search Strategies (PRESS) checklist [28], and it is presented in the online Supplementary Materials. Supplemental searches were conducted as per our protocol, and references cited in included studies and related reviews were also scanned. Eligibility screening, data extraction, and risk-of-bias appraisals were done independently in duplicate. The original Cochrane Risk-of-Bias tool [29] was used for RCTs, and the Newcastle-Ottawa Scale [30] was used to assess the methodological quality of nonrandomized and observational studies. Relative risk (RR) for binary outcomes and mean difference (MD) for continuous outcomes were calculated for each trial along with 95% confidence intervals (CIs), when appropriate. Forest plots were created to graphically display data using RevMan 5.4.1, when appropriate [31]. Meta-analysis was not conducted due to the high heterogeneity observed across the very diverse interventions evaluated with respect to different probiotic combinations, genera, species, and strains that each have unique properties and potential effects [17]. Following the Cochrane Handbook and Synthesis Without Meta-analysis (SWiM) guidance, the vote counting of direction of effect method was used for synthesis [24,32]. This method does not provide information about effect size or evaluate statistical significance and is intended to explore trends among studies, so summary results presented across the RCTs necessitate careful interpretation.

3. Results

3.1. Included Studies

Searches for the overarching umbrella project of 10 natural health products retrieved 4653 records in total, which were screened in duplicate. A total of 45 probiotics articles were included, reporting on 42 unique studies, comprising 39 reports (listed alphabetically under the References) [33–71], of 36 randomized controlled trials involving 3305 participants and 6 nonrandomized and cohort studies [72–77]. A study flow diagram is presented in Figure 1.
Figure 1. Study flow diagram.

The interventions and comparators evaluated in the 36 included RCTs are presented in Table 1, including dosage and administration details. Supplemental Table S1 provides the interventions and exposures assessed in the six nonrandomized and observational cohort studies. Table 2 reports the study and patient characteristics of the RCTs; and characteristics of the nonrandomized and observational studies are found in the Supplementary Materials (Table S2). Table S3 provides an overview of the summary characteristics across the 36 RCTs. All except 2 RCTs (94%) dealt with digestive system cancers, and one each was on bladder and head and neck cancers. Roughly half of the RCTs dealt with colorectal cancer (19 RCTs; 53%), followed by hepatobiliary/pancreatic as the second most common cancer types (8 RCTs; 22%). A total of 81% of the included RCTs (29/36) evaluated multi-strain formulations, with a wide variety of bacteria combinations studied. 21 diverse formulations were evaluated, with 42% of the RCTs (15/36) studying unique products (i.e., product included in one RCT). Figure S1 details the six probiotic products and their components that were utilized in more than one RCT. 83% of RCTs (30/36) investigated oral products, while six (16%) administered interventions by enteral nutrition tubes. More than half the RCTs (20/36; 56%) administered the probiotics during both the pre- and post-operative periods, while nine RCTs (25%) utilized them only preoperatively, and in seven RCTs (19%) they were given only postoperatively. A total of 53% of RCTs (19/36) were conducted in Asia, and 31% (11 RCTs) were from Europe. A total of 72% of RCTs were published in the last 10 years (26/36).
### Table 1. Interventions and comparators evaluated in 36 included RCTs.

| Author Year | Interventions and Comparators with Dosages | Freq. of Dose | Route of Tx | Duration | Tx Duration | Tx Duration | Tx Duration |
|-------------|-------------------------------------------|---------------|-------------|----------|-------------|-------------|-------------|
| Anderson 2004 [33] | Lactobacillus acidophilus La5 + L. bulgaricus + Bifidobacterium lactis Bb-12 + Streptococcus thermophilus (4 billion CFU) capsule + oligofructose (11 g) powder | TID oral | Admin. Pre-op (Days) 12 | 4 | 16 |
| | Placebo capsule + sucrose placebo powder | TID oral | 12 | 4 | 16 |
| Aso 1992 [34] | Lactobacillus casei (10 billion viable cells) | TID oral | NA | 365 | 365 |
| | Standard care alone | NA | NA |
| Cho 2019 [35] | Lactobacillus plantarum CJLP243 (10 billion) | QD oral | 1 | 21 | 22 |
| | Maltodextrin + glucose placebo (2 g) | QD oral | 1 | 21 | 22 |
| Consoli 2016 [36] | Saccharomyces boulardii (50 million CFU) | QD oral | 9 | NA | 9 |
| Diepenhorst 2011 [37] | Bifidobacterium bifidum + B. infantis + Lactobacillus acidophilus + L. casei + L. salivarius + L. lactis (10 billion) | BID oral | 7 | 7 | 14 |
| | Standard tx control b [neither probiotics nor SDD] | NR | NA | NR | NR |
| | Selective decontamination of the digestive tract (SDD antibiotics regimen) | 4 times daily | Multiple | 4 | 2 | 6 |
| Flesch 2017 [38] | Lactobacillus acidophilus NCFM + L. rhamnosus HN001 + L. paracasei LPC-37 + Bifidobacterium lactis HN019 (1 billion CFU each) + fructooligosaccharides * (6 g) | BID oral | 5 | 14 | 19 |
| | Maltodextrin placebo (6 g) | BID oral | 5 | 14 | 19 |
| Franko 2019 [39] | Bifidobacterium breve + B. longum + B. infantis + Lactobacillus acidophilus + L. plantarum + L. paracasei + L. bulgaricus + Streptococcus thermophilus (112.5 billion CFU/capsule) | BID oral | 1 | 6 | 7 |
| | Placebo | BID oral | 1 | 6 | 7 |
| Horvat 2010 [40] | Pediacoccus pentosaceus 5–33:3 + Leuconostoc mesenteroides 32–77:1 + Lactobacillus paracasei subsp. paracasei 19 + L. plantarum 2362 (10 billion each) + betaglucan + inulin + pectin + resistant starch fibers * (2.5 g each) [without mechanical bowel preparation] | BID oral | 3 | NA | 3 |
| | Mechanical bowel preparation control b | QD oral | 1 | NA | 1 |
| | Heat-inactivated lactobacilli + betaglucan + inulin + pectin + resistant starch fibers (2.5 g each) [without mechanical bowel preparation] | BID oral | 3 | NA | 3 |
| Kanazawa 2005 [41] | Lactobacillus casei strain Shirota (300 million) + Bifidobacterium breve strain Yakult (300 million) + galactooligosaccharides * (12 g) + EN + PN | QD enteral | NA | 14 | 14 |
| | Standard EN + PN | QD NA | NA | 14 | 14 |
| Komatsu 2016 [42] | Lactobacillus casei strain Shirota (40 billion) + Bifidobacterium breve strain Yakult (10 billion) + galactooligosaccharides * (2.5 g) | QD oral | 7–11 | Yes | Total NR |
| | Standard care alone | NA | NA | |
| Kotzampassi 2015 [43] | Lactobacillus acidophilus LA-5 (1.75 billion CFU) + L. plantarum (0.5 billion CFU) + Bifidobacterium lactis BB-12 (1.75 billion CFU) + Saccharomyces boulardii (1.5 billion CFU) | BID oral | 1 | 15 | 16 |
| | Glucose polymer placebo | BID oral | 1 | 15 | 16 |
| Krebs 2016 [45] | Pediacoccus pentosaceus 5–33:3 + Leuconostoc mesenteroides 32–77:1 + Lactobacillus paracasei subsp. | BID oral | 3 | NA | 3 |
| Study | Treatment  | Control  | Dose | Route | Duration | Notes |
|-------|------------|----------|------|-------|----------|-------|
| Lages 2018 [46] | *L. paracasei* 19 + *L. plantarum* 2362 (100 billion each) + betaglucan + inulin + pectin + resistant starch fibers *2.5 g each* [without mechanical bowel preparation] | Mechanical bowel preparation control | QD oral | 1 NA 1 | |
|       | *Betaglucan* + *inulin* + *pectin* + *resistant starch fibers* *2.5 g each* [without mechanical bowel preparation] | | | | |
|       | *Lactobacillus paracasei* LPC-31 + *L. rhamnosus* HN001 + *L. acidophilus* NCFM + *Bifidobacterium lactis* HN019 (1 billion CFU/mL each) + fructooligosaccharides *6 g* diluted in 20 mL of water + standard EN | | | | |
|       | Maltodextrin placebo (6 g) + standard EN | | | | |
| Liu 2015 [49] | *Lactobacillus plantarum* CGMCC No. 1258 (200 billion CFU) + *L. acidophilus* LA-11 (140 billion CFU) + *Bifidobacterium longum* BL-88 (100 billion CFU) | | | | |
| Mangell 2012 [50] | *Lactobacillus plantarum* 299v (100 billion CFU) in an oatmeal-based drink *2 (100 mL)* | | | | |
|       | *Oatmeal-based placebo drink without probiotics* (100 mL) | | | | |
| McNaught 2002 [51] | *Lactobacillus plantarum* 299v (25 billion CFU/day) in an oatmeal-based drink * | | | | |
| Nomura 2007 [52] | *Enterococcus fecalis* T-110 (12 mg/day) + *Clostridium butyricum* TO-A (60 mg/day) + *Bacillus mesentericus* TO-A (60 mg/day) | | | | |
| Okazaki 2013 [53] | *Lactobacillus casei* strain Shirota (1 g) + *Bifidobacterium breve* strain Yakult (1 g) + galactooligosaccharides *15 g* | | | | |
| Park 2020 [54] | *Bifidobacterium animalis* subsp. *lactis* HY8002 (100 million CFU) + *Lactobacillus casei* HY2782 (50 million CFU) + *L. plantarum* HY7712 (50 million CFU) + xylooligosaccharides (350 mg) + fructooligosaccharides (36 mg) | | | | |
|       | *Xylooligosaccharides* (350 mg) + fructooligosaccharides (36 mg) | | | | |
| Polakowski 2019 [55] | *Lactobacillus acidophilus* NCFM + *L. rhamnosus* HN001 + *L. paracasei* LPC-37 + *Bifidobacterium lactis* HN019 (1 billion each) + fructooligosaccharides *6 g* | | | | |
| Rayes 2002 [56] | *Live Lactobacillus plantarum* 299 (1 billion) + oat fiber *11.3 g/L* + EN | | | | |
|       | Standard total parenteral nutrition or fiber-free EN control | | | | |
|       | *Heat-killed Lactobacillus plantarum* 299 + oat fiber (11.3 g/L) + EN | | | | |
| Rayes 2007 [57] | *Pediococcus pentosaceus* 5:33:3 + *Leuconostoc mesenteroides* 32–77:1 + *Lactobacillus paracasei* subsp. *paracasei* 19 + *L. plantarum* 2362 (10 billion) + betaglucan + inulin + pectin + resistant starch fibers | | | | |
| Study                  | Pre-op                                      | Post-op                                    | Probiotics and Preparations                                                                 | Route                                      | Doses (in billion CFU) | Notes                                                                 |
|------------------------|---------------------------------------------|--------------------------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------|------------------------|----------------------------------------------------------------------|
| Reddy 2007 [59]        |                                            |                                            | Betaglucan + inulin + pectin + resistant starch fibers (2.5 g each) + EN BID enteral 1 8 9      |                                            |                        |                                                                      |
| Redyes 2012 [58]       | Betaglucan + inulin + pectin + resistant starch fibers (2.5 g each) + EN BID enteral 1 10 11 | Lactobacillus acidophilus La5 + L. bulgaricus + Bifidobacterium lactis Bb-12 + Streptococcus thermophilus (4 billion CFU) + oligofructose + neomycin (3 g) + mechanical bowel preparation | TID oral NR NA NR                          |                                            |                        |                                                                      |
|                        | Pediacoccus pentosaceus 5–33:3 + Leuconostoc mesenteroides 32–77:1 + Lactobacillus paracasei subsp. paracasei 19 + L. plantarum 2362 (10 billion) + betaglucan + inulin + pectin + resistant starch fibers (2.5 g each) + EN | Neomycin (3 g) + mechanical bowel preparation control |                                                                                               |                                            |                        |                                                                      |
|                        |                                             |                                            |                                                                                               |                                            |                        |                                                                      |
| Sadahiro 2014 [60]     | Standard care alone control b [plus single IV dose of flomoxef; & standard mechanical bowel preparation] | Lactobacillus acidophilus La5 + L. bulgaricus + Bifidobacterium lactis Bb-12 + Streptococcus thermophilus (4 billion CFU) + oligofructose (10 g) + neomycin (3 g) [without mechanical bowel preparation] | TID oral NR NA NR                          |                                            |                        |                                                                      |
|                        |                                            |                                            |                                                                                               |                                            |                        |                                                                      |
| Sommacal 2015 [61]     | Mechanical bowel preparation only QD oral 1 NA 1 | Bifidobacterium bifidum (3.3 billion) + maltooligosaccharide [plus single IV dose of flomoxef; & standard mechanical bowel preparation] | TID oral 7 10 17                          |                                            |                        |                                                                      |
|                        |                                            |                                            |                                                                                               |                                            |                        |                                                                      |
| Sugawara 2006 [62]     | Pre-op: Oral Lactobacillus casei strain Shirota (40 billion) + Bifidobacterium breve strain Yakult (10 billion) + galactooligosaccharides (15 g). | Post-op: Lactobacillus casei strain Shirota (300 million) + Bifidobacterium breve strain Yakult (300 million) + galactooligosaccharides (15 g) + standard EN + PN. | QD oral & enteral 14 14 28               |                                            |                        |                                                                      |
|                        |                                            |                                            |                                                                                               |                                            |                        |                                                                      |
| Tan 2016 [63]          | Pre-op: Standard care alone.                | Post-op: Lactobacillus casei strain Shirota (300 million) + Bifidobacterium breve strain Yakult (300 million) + galactooligosaccharides (15 g) + standard EN + PN. | QD enteral NA 14 14                       |                                            |                        |                                                                      |
|                        |                                            |                                            |                                                                                               |                                            |                        |                                                                      |
| Usami 2011 [64]        | Lactobacillus acidophilus BCMC12130 + L. casei BCMC12313 + L. lactis BCMC12451 + Bifidobacterium bifidum BCMC02290 + B. longum BCMC02120 + B. infantis BCMC02129 (30 billion CFU) | Placebo (3 g) | BID oral 7 NA 7                          |                                            |                        |                                                                      |
|                        |                                            |                                            |                                                                                               |                                            |                        |                                                                      |
|                        |                                            |                                            |                                                                                               |                                            |                        |                                                                      |
| Study | Interventions                                                                 | Administration | Duration | Placebo Administration |
|-------|-------------------------------------------------------------------------------|----------------|----------|-------------------------|
| Xu 2019 [65] | **Post-op:** Standard care alone [+ PN for 4 days post-op]                  | NA             | NA       | NA                      |
|        | Bifidus-triple viable preparation + glucose solution                               | QD oral        | 7        | NA                      |
|        | Glucose solution                                                                  | QD oral        | 7        | NA                      |
| Yang 2016 [66] | **Post-op:** Bifidobacterium longum + Lactobacillus acidophilus + Enterococcus faecalis * (20 million CFU each) | TID oral       | 5        | 7                       |
|        | Maltodextrin + sucrose placebo (2 g)                                             | TID oral       | 5        | 7                       |
| Yokoyama 2014 [67] | **Pre-op:** Oral or enteral Lactobacillus casei strain Shirota (40 billion) + Bifidobacterium breve strain Yakult (10 billion) + galactooligosaccharides * (15 g).<br>**Post-op:** Enteral Lactobacillus casei strain Shirota (300 million) + Bifidobacterium breve strain Yakult (300 million) + galactooligosaccharides (15 g) + EN. | QD oral & enteral | 7 | 14  |
|        | **Pre-op:** Standard care alone (ordinary diet).<br>**Post-op:** Standard EN.       | QD enteral     | 7        | 14                      |
| Yokoyama 2016 [68] | **Pre-op:** Oral Lactobacillus casei strain Shirota (40 billion) + Bifidobacterium breve strain Yakult (10 billion) + galactooligosaccharides * (15 g).<br>**Post-op:** Enteral Lactobacillus casei strain Shirota (300 million) + Bifidobacterium breve strain Yakult (300 million) + galactooligosaccharides (15 g) + EN. | QD oral & enteral | 7 | 14  |
| Zhang 2012 [69] | **Pre-op:** Bifidobacterium longum + Lactobacillus acidophilus + Enterococcus faecalis * (63 million CFU) | TID oral       | 3        | NA                      |
|        | Maltodextrin placebo                                                              | TID oral       | 3        | NA                      |
| Zhao 2017 [70] | **Post-op:** Bifidobacterium + Lactobacillus (6 g) + fiber + (30 g) + EN<br>**Fiber-free EN control** | QD enteral     | NA       | 7                       |
|        | **Fiber-enriched EN (with 30 g of Shen Jia™ fiber)**                              | QD enteral     | NA       | 7                       |
| Zheng 2019 [71] | **Pre-op:** Bifidobacterium infantis (3 million CFU) + Lactobacillus acidophilus (3 million CFU) + Enterococcus faecalis (3 million CFU) + Bacillus cereus (300,000 CFU) | TID oral       | NA       | 6–7                     |
|        | Placebo                                                                         | TID oral       | NA       | 6–7                     |

**Notes:**
- BID = twice daily, CFU = colony forming units, EN = enteral nutrition, IQR = interquartile range, med. = median, NA = not applicable, NR = not reported, PN = parenteral nutrition, QD = once daily, TID = 3 times daily, Tx = treatment.
- a, This probiotics formulation was studied in more than one RCT (see Figure 2). b, This group was the control arm in the forest plot(s). c, Product brand name is Simbioflora™ (Farmoquimica, Sao Paulo, Brazil). The RCT report lists one of the components as “L. casei LPC-37”, but an Internet product search revealed it might be “L. paracasei LPC-37”. d, Probiotics were sourced from Atlantic Essential Products (Hauppauge, NY, USA) and prebiotics from Future Ceuticals (Momence, IL, USA). e, Further ingredient details not reported (Inner Mongolia Shuangqi Pharmaceutical Co. Ltd., Inner Mongolia, China). f, Shen Jia™ fiber (ingredient(s) not reported; Beijing Tianqian Yikang Biological Technology Corp. Ltd., Beijing, China). Abbreviations: BI = twice daily, CFU = colony forming units, EN = enteral nutrition, IQR = interquartile range, med. = median, NA = not applicable, NR = not reported, PN = parenteral nutrition, QD = once daily, TID = 3 times daily, Tx = treatment.
Table 2. Study and patient characteristics of 36 included RCTs.

| Author           | Year       | Sample Size | Country   | Study Period | Cancer Types                                  | Funding  | Female (%) | Age Mean (years) | Age Variance |
|------------------|------------|-------------|-----------|--------------|-----------------------------------------------|----------|-------------|------------------|--------------|
| Anderson         | 2004 [33]  | 137         | UK        | NR           | Colon (majority) & other GI cancers           | NR       | 48          | 69               | NR           |
| Aso              | 1992 [34]  | 48          | Japan     | 1988–1990    | Bladder cancer                                | NR       | 13          | NR               | NR           |
| Cho              | 2019 [35]  | 36          | South Korea | 2016–2017  | Rectal cancer                                 | public   | NR          | NR               | NR           |
| Consoli          | 2016 [36]  | 68          | Brazil    | 2010–2013    | Colon cancer                                  | public   | 55          | 55               | Range 17–83  |
| Diepenhorst      | 2011 [37]  | 30          | The Nether-lands | 2005–2006 | Periampullary & ampullary pancreatic cancers | NR       | 50          | 61               | NR           |
| Flesch           | 2017 [38]  | 91          | Brazil    | 2013–2015    | Colorectal cancer                             | none     | 59          | 63               | NR           |
| Franko           | 2019 [39]  | 135         | USA       | 2015–2017    | Colorectal (70%), hepato-biliary & pancreatic cancers | public   | 51          | 62.5             | SD 12.1      |
| Horvat           | 2010 [40]  | 76          | Slovenia  | NR           | Colorectal cancer                             | unclear  | 59          | 63               | Range 29–86  |
| Kanazawa         | 2005 [41]  | 54          | Japan     | 2000–2002    | Biliary cancers                               | NR       | 34          | 64               | NR           |
| Komatsu          | 2016 [42]  | 379         | Japan     | 2008–2014    | Colorectal cancer                             | private  | 42          | 68               | NR           |
| Kotzampassi      | 2015 [43]  | 168         | Greece    | 2013–2014    | Colorectal cancer                             | unclear  | 30          | 66               | NR           |
| Krebs            | 2016 [45]  | 60          | Slovenia  | 2009–2012    | Colorectal cancer                             | NR       | 39          | 65               | Range 43–87  |
| Lages            | 2018 [46]  | 40          | Brazil    | 2014–2016    | Head & neck cancers                           | public   | 19          | 60.5             | NR           |
| Liu              | 2015 [49]  | 161         | China     | 2007–2013    | Colorectal cancer                             | public   | 48          | 63               | NR           |
| Mangell          | 2012 [50]  | 72          | Sweden    | NR           | Colon cancer                                  | public   | 44          | 72               | NR           |
| McNaught         | 2002 [51]  | 129         | UK        | NR           | Colorectal (51%) & other GI cancers           | NR       | 42          | 69               | NR           |
| Nomura           | 2007 [52]  | 70          | Japan     | 2004–2006    | Pancreatic biliary cancers                    | NR       | 39          | 68               | Range 30–88  |
| Okazaki          | 2013 [53]  | 48          | Japan     | 2009–2011    | GI (88%) & hepatobiliary pancreatic cancers   | NR       | 46          | 79               | Range 70–92  |
| Park             | 2020 [54]  | 68          | South Korea | 2016–2018  | Sigmoid colon cancer                          | private  | 47          | 61               | NR           |
| Polakowski       | 2019 [55]  | 73          | Brazil    | NR           | Colorectal cancer                             | NR       | 47          | 60               | NR           |
| Rayes            | 2002 [56]  | 90          | Germany   | 1997–1999    | Hepatic (32%), pancreatic (29%), gastric (24%) & colon cancers | NR       | 47          | 61               | NR           |
| Rayes            | 2007 [57]  | 89          | Germany   | NR           | Pancreatic cancer                             | NR       | 44          | 58.5             | NR           |
| Rayes            | 2012 [58]  | 19          | Germany   | 2007–2008    | Colorectal metastasis (53%), cholangiocellular carcinoma (42%) & liver cancers | NR       | 26          | 60               | NR           |
| Reddy            | 2007 [59]  | 92          | UK        | NR           | Colorectal cancer                             | private  | 50          | 69               | NR           |
| Sadahiro         | 2014 [60]  | 310         | Japan     | 2008–2011    | Colon cancer                                  | private  | 47          | 67               | NR           |
| Sommacal         | 2015 [61]  | 48          | Brazil    | 2010–2012    | Periampullary cancers                         | public   | NR          | 59               | Range 44–85  |
| Author       | Year | Country    | Year_range | Type of cancer          | Source          | Patients | 5-year OS | 10-year OS | Range |
|--------------|------|------------|------------|-------------------------|-----------------|----------|-----------|------------|-------|
| Sugawara     | 2006 | Japan      | 2003–2005  | Biliary cancers         | NR              | 43       | 63        | NR         |       |
| Tan 2016     | [63] | Malaysia   | 2012–2013  | Colorectal cancer       | private         | 40       | 66        | NR         |       |
| Usami 2011   | [64] | Japan      | 2005–2008  | Hepatic cancer          | mixed public & private | 10       | 65        | NR         |       |
| Xu 2019 [65] |      | China      | 2017–2018  | Colorectal cancer       | none            | 37       | NR        | NR         |       |
| Yang 2016    | [66] | China      | 2011–2012  | Colorectal cancer       | public          | 55       | 63        | NR         |       |
| Yokoyama 2014| [67] | Japan      | 2008–2011  | Esophageal cancer       | private         | 12       | 65.5      | Range 25–77|       |
| Yokoyama 2016| [68] | Japan      | 2010–2012  | Pancreatic & biliary cancers | private     | 73       | 65        | Range 41–83|       |
| Zhang 2012   | [69] | China      | 2006–2007  | Colorectal cancer       | public          | 60       | 65        | Range 45–87|       |
| Zhao 2017    | [70] | China      | 2015–2016  | Gastric cancer          | public          | 48       | 66        | NR         |       |
| Zheng 2019   | [71] | China      | 2017–2018  | Gastric cancer          | public          | 16       | 62        | NR         |       |

**Abbreviations:** GI = gastrointestinal, NR = not reported, SD = standard deviation.
| Study          | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|---------------|-------------------------------------------|----------------------------------------|--------------------------------------------------------|-----------------------------------------------|----------------------------------------|-----------------------------------|------------|
| Anderson 2004 | ?                                        | +                                      | +                                                      | +                                             | ?                                      | +                                 |            |
| Aso 1992      | ?                                        | ?                                      | -                                                      | -                                             | +                                      | +                                 |            |
| Cho 2019      | ?                                        | ?                                      | +                                                      | +                                             | +                                      | ?                                 |            |
| Consoli 2016  | ?                                        | ?                                      | -                                                      | -                                             | ?                                      | +                                 |            |
| Diepenhorst 2011 | +                           | ?                                      | ?                                                      | ?                                             | +                                      | ?                                 | +          |
| Flesch 2017   | +                                        | +                                      | +                                                      | +                                             | -                                      | -                                 |            |
| Franko 2019   | ?                                        | ?                                      | +                                                      | ?                                             | +                                      | +                                 |            |
| Horvat 2010   | +                                        | ?                                      | ?                                                      | +                                             | ?                                      | +                                 |            |
| Kanazawa 2005* | ?                                  | ?                                      | +                                                      | +                                             | ?                                      | +                                 |            |
| Komatsu 2016  | +                                        | +                                      | -                                                      | -                                             | +                                      | +                                 |            |
| Kotzampassi 2015 | +                     | +                                      | +                                                      | +                                             | +                                      | +                                 |            |
| Krebs 2016*   | ?                                        | +                                      | +                                                      | +                                             | ?                                      | +                                 |            |
| Lages 2018    | ?                                        | ?                                      | +                                                      | +                                             | +                                      | +                                 |            |
| Liu 2015      | +                                        | +                                      | +                                                      | +                                             | +                                      | +                                 |            |
| Mangell 2012  | ?                                        | ?                                      | +                                                      | +                                             | ?                                      | +                                 |            |
| McNaught 2002 | +                                        | ?                                      | -                                                      | -                                             | +                                      | ?                                 |            |
| Nomura 2007*  | ?                                        | ?                                      | +                                                      | +                                             | ?                                      | +                                 |            |
| Okazaki 2013  | ?                                        | +                                      | -                                                      | +                                             | ?                                      | +                                 |            |
| Park 2020     | +                                        | +                                      | +                                                      | +                                             | ?                                      | +                                 |            |
| Polakowski 2019 | +                          | +                                      | +                                                      | +                                             | ?                                      | +                                 |            |
| Rayes 2002    | ?                                        | ?                                      | -                                                      | -                                             | +                                      | ?                                 |            |
| Rayes 2007    | ?                                        | ?                                      | +                                                      | +                                             | ?                                      | +                                 |            |
| Rayes 2012    | ?                                        | ?                                      | +                                                      | +                                             | ?                                      | +                                 |            |
| Reddy 2007*   | ?                                        | ?                                      | +                                                      | +                                             | ?                                      | +                                 |            |
| Sadahiro 2014* | +                                 | +                                      | +                                                      | +                                             | +                                      | +                                 |            |
| Sommacal 2015 | +                                        | ?                                      | +                                                      | +                                             | ?                                      | +                                 |            |
| Sugawara 2006 | ?                                        | ?                                      | -                                                      | -                                             | +                                      | ?                                 |            |
| Tan 2016      | +                                        | +                                      | +                                                      | +                                             | +                                      | +                                 |            |
| Usami 2011    | ?                                        | +                                      | -                                                      | -                                             | +                                      | ?                                 |            |
| Xu 2019       | ?                                        | ?                                      | ?                                                      | ?                                             | ?                                      | ?                                 |            |
| Yang 2016     | +                                        | ?                                      | +                                                      | +                                             | ?                                      | +                                 |            |
| Yokoyama 2014* | +                                 | +                                      | +                                                      | +                                             | ?                                      | +                                 |            |
| Yokoyama 2016* | +                                 | +                                      | +                                                      | +                                             | +                                      | +                                 |            |
| Zhang 2012    | ?                                        | ?                                      | +                                                      | +                                             | ?                                      | +                                 |            |
| Zhao 2017     | +                                        | ?                                      | -                                                      | ?                                             | +                                      | ?                                 |            |
| Zheng 2019    | +                                        | ?                                      | +                                                      | ?                                             | -                                      | +                                 |            |

Figure 2. Risk-of-bias appraisal of each RCT. Green “+” = low risk; yellow “?” = unclear risk; red “-” = high risk of bias. * These 7 RCTs had no/unclear blinding but only reported objective outcomes.
3.2. Risk-of-Bias Appraisal

Results for each study of the RCT risk-of-bias assessments using the Cochrane tool are presented in Figure 2, and the aggregate summary results of the 36 RCTs are in Figure 3. A substantial risk-of-bias was found across the majority of RCTs, with only five RCTs (14%) judged as low risk-of-bias on the seven assessment elements in these methodological quality appraisals: Franko et al., 2019; Kotzampassi et al., 2015; Liu et al., 2015; Sadahiro et al., 2014; Tan et al., 2016 [39,43,49,60,63]. Selective reporting (reporting bias) and allocation concealment were the risk-of-bias elements that scored worst. Furthermore, roughly half of the RCTs did not adequately report on random sequence generation, suggesting potential selection bias. Additionally, roughly one-third of RCTs were unclear or high risk for the elements on blinding of participants and personnel and blinded outcome assessment, which suggest potential performance and detection biases.

![Figure 3. Aggregate risk-of-bias across RCTs. Green = low risk; yellow = unclear risk; red = high risk of bias.](image)

3.3. Mortality and Recurrence

The primary outcome of mortality was assessed in 23 RCTs, of which 12 reported that there were no deaths [36,41,42,46,49,56,59,62,64,66,69]. Absolute number of events, sample size, and relative risks with 95% CIs for each of the 11 RCTs that reported deaths are presented visually in a forest plot (Figure 4). There was conflicting evidence of any effect on mortality, with 7 of 11 RCTs (64%) favoring probiotics (one had sparse data) based on direction of effect [33,39,50,52,55,61,63], while one (10%) showed no effect [57]. However, three RCTs (20%) favored controls, including the McNaught 2002 trial finding a risk of 30-day mortality of RR 3.55 (95% CI: 0.77, 16.47) in the probiotics group (7/64; 11%) vs. controls (2/65; 3%). Of note, however, this trial amended its protocol after 11 probiotics patients had already been enrolled to also give the probiotics arm antibiotic prophylaxis (the initial comparison was intended to be probiotics vs. antibiotics), yet mortality data was only reported including these 11 patients who had not received antibiotics preoperatively. This trial administered *Lactobacillus plantarum* 299v + oatmeal to patients undergoing colorectal and abdominal surgeries [51]. The other 2 RCTs by Yokoyama et al., 2014 and Yokoyama et al., 2016 had sparse data (i.e., only one death in total occurred in each trial) [67,68]. An additional RCT presented results graphically for alive hospital discharges at 31 days showing almost all participants in the probiotics group compared to roughly 10% fewer in controls [43].
Only one RCT reported on cancer recurrence. Assessed in superficial bladder cancer surgery, the probiotics group had a 1.8-times-longer 50% recurrence-free interval than controls ($p = 0.03$) [34]. None of the RCTs reported data on the other primary outcomes of our review (i.e., hard treatment endpoints).

| Study or Subgroup | Probiotics Events Total | Control Events Total | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|-------------------|-------------------------|----------------------|-------------------------------|-------------------------------|
| Anderson 2004     | 5 72                    | 9 85                 | 0.50 [0.16, 1.42]             |                               |
| Frank 2010        | 1 67                    | 2 66                 | 0.51 [0.05, 5.46]             |                               |
| Mangelli 2012     | 1 32                    | 2 32                 | 0.59 [0.05, 5.92]             |                               |
| McHenry 2002      | 7 84                    | 2 85                 | 3.56 [0.77, 15.47]            |                               |
| Nomura 2007       | 0 36                    | 1 34                 | 0.33 [0.02, 6.91]             |                               |
| Polakowska 2019   | 0 36                    | 3 37                 | 0.19 [0.01, 3.74]             |                               |
| Reyes 2007        | 1 46                    | 1 40                 | 1.06 [0.05, 20.44]            |                               |
| Sharma 2015       | 0 23                    | 6 23                 | 0.69 [0.06, 7.29]             |                               |
| Tan 2010          | 0 21                    | 2 20                 | 0.20 [0.01, 3.02]             |                               |
| Yokoyama 2014     | 1 21                    | 0 21                 | 3.06 [0.13, 65.71]            |                               |
| Yokoyama 2015     | 1 22                    | 0 22                 | 3.06 [0.13, 65.71]            |                               |

Figure 4. Forest plot for mortality ($n = 11$ RCTs).

3.4. Postoperative Infections

Thirty RCTs reported on total postoperative infections, which are presented in a forest plot (Figure 5). Across these studies, there was evidence based on direction of effect that probiotics had a beneficial effect on postoperative infections, with 21 of 30 RCTs (70%) favoring them (one had sparse data), while another four (13%) showed no effect. In contrast, five RCTs (17%) favored controls [37,46,58,67,68]. The Lages et al., 2018 trial found a postoperative infection risk of RR 1.57 (95% CI: 0.79, 3.12) in the probiotics group vs. controls (11/18 vs. 7/18), and this trial in head and neck cancers administered *Lactobacillus acidophilus* NCFM + *L. rhamnosus* HN001 + *L. paracasei* LPC-31 + *Bifidobacterium lactis* HN019 + fructooligosaccharides [46]. Yokoyama et al., 2014 found a RR 1.50 (95% CI: 0.65, 3.47) [67]. The other three negative RCTs had wide confidence intervals (one had sparse data).
In addition, bacteremia/sepsis data were evaluated for safety as a specific subgroup of severe postoperative infectious complications, which were reported on in 12 of the above RCTs (Table S4). This revealed that two RCTs (17%) found higher rates in the probiotics group compared to controls. Yokoyama et al., 2014 had two cases (RR 5.00; 95% CI: 0.25, 98.27; 2/21 vs. 0/21) [67]; and another trial had one additional central line infection (RR 1.20; 95% CI: 0.43, 3.39; 7/66 vs. 6/68) [49]. Furthermore, since most studies were found to be on gastrointestinal cancer surgeries, a post-hoc analysis is presented on the RCTs that specifically reported a breakdown of anastomotic leakage/abdominal abscess subgroup type of infections (Table S4). Only 1 out of 16 (6%) RCTs (Yokoyama et al., 2014 [67]) found a higher rate of these events in the probiotics compared to control groups.

Corresponding to the infections results, there was evidence that probiotics had a beneficial effect on the length of antibiotic therapy, with seven of seven RCTs (100%) favoring them. All seven studies are included in the infections outcome above. Figure 6 presents a forest plot of the mean difference in days for each RCT.

**Figure 5.** Forest plot for infections (n = 30 RCTs).

**Figure 6.** Forest plot for antibiotics duration of use, in days (n = 7 RCTs).
3.5. Ileus and Intestinal Obstruction

Postoperative ileus or intestinal obstruction comparative results were evaluated in seven RCTs (forest plot details presented in Figure 7). Evidence was unclear for any effect of probiotics on ileus or intestinal obstruction. Four of seven RCTs (57%) favored probiotics (two had sparse data), while one (14%) with sparse data favored controls (one event total) [50], and two RCTs (29%) showed no effect.

| Study or Subgroup | Probiotics Events Total | Control Events Total | Risk Ratio IV, Random, 95% CI |
|-------------------|------------------------|----------------------|-------------------------------|
| Corsell 2018      | 0                      | 16                   | 0.40 (0.02, 0.96)             |
| Dinnissen 2011    | 1                      | 16                   | 1.00 (0.01, 10.97)            |
| Komatsu 2015      | 7                      | 194                  | 0.81 (0.31, 2.08)             |
| Kungell 2012      | 1                      | 32                   | 3.40 (0.15, 71.90)            |
| Okazaki 2013      | 3                      | 26                   | 0.68 (0.17, 2.76)             |
| Park 2020         | 0                      | 29                   | 0.36 (0.02, 0.36)             |
| Zhang 2012        | 3                      | 30                   | 0.50 (0.14, 1.82)             |

Figure 7. Forest plot for ileus or intestinal obstruction (n = 7 RCTs).

3.6. Diarrhea

Comparative results on diarrhea were assessed in seven RCTs, of which two had no cases [37,56]. There was conflicting evidence of any effect on diarrhea, as three of five RCTs (60%) favored probiotics (one had sparse data), while one (20%) showed no effect (forest plot in Figure 8). However, one RCT (20%) by Anderson et al., 2004 favored controls, with an increased risk of diarrhea of RR 8.14 (95% CI: 0.45, 148.28) for probiotics (4/72; 6%) vs. controls (0/65). This trial dealt with colon cancer and other abdominal surgeries and used a combination of Lactobacillus acidophilus La5 + L. bulgaricus + Bifidobacterium lactis Bb-12 + Streptococcus thermophilus + oligofructose [33].

| Study or Subgroup | Probiotics Events Total | Control Events Total | Risk Ratio IV, Random, 95% CI |
|-------------------|------------------------|----------------------|-------------------------------|
| Anderson 2004     | 4                      | 72                   | 0.14 (0.45, 14.20)            |
| Park 2020         | 0                      | 29                   | 0.39 (0.02, 0.39)             |
| Yang 2007         | 2                      | 49                   | 1.00 (0.15, 6.70)             |
| Yang 2016a        | 8                      | 39                   | 0.59 (0.25, 0.99)             |
| Zhao 2017         | 2                      | 40                   | 0.89 (0.02, 0.33)             |

Figure 8. Forest plot for diarrhea (n = 5 RCTs).

3.7. White Blood Cells and C-Reactive Protein

Leukocyte counts were assessed in 12 RCTs. Details are reported in Supplementary Materials Table S4. The evidence was unclear for any effect on total white blood cells (WBCs) as seven RCTs (58%) showed no effect and three (25%) favored probiotics, while two RCTs (17%) [67,68], favored controls. Similarly, the effect was unclear for lymphocytes reported on in six RCTs, with three RCTs (50%) showing no effect and two (33%) favoring probiotics, while one RCT (17%) [56], favored controls (Table S4). Neutrophil counts were reported on in only three RCTs, and no effect was seen from probiotics compared to baseline. The evidence was also unclear for any effect on C-reactive protein levels reported on in 13 RCTs, with six of them showing no effect and three favored probiotics, whereas four RCTs (31%) [33,40,51,68] favored controls (Table S4).

3.8. Hospital Length of Stay

Duration of hospitalization details are presented for 22 RCTs in Table S4. 19 of these studies are also included in the infections outcome (Figure 5), which is a major contributing factor for length of stay. For the other three RCTs, the number of days in hospital was fairly similar between groups [45,68,70].
3.9. Additional Outcomes

Eleven RCTs utilizing probiotics preoperatively reported on blood loss (Table S4). Two (18%) RCTs found more blood loss in the probiotics groups; however, in both trials, mean operative times were 1 h longer and they reported more extensive resection/dissection occurred in the probiotics groups [64,67]. Pain was evaluated in seven RCTs (six on abdominal pain/cramps and one reporting pain scores). The evidence was unclear for any effect on pain with five RCTs showing no effect and two favored probiotics (Table S4). Two RCTs reported comparative results between groups on nausea/vomiting; one found a greater increase on a nausea score (FACT-G7 subscale) in the probiotics group vs. placebo [39], while the other had fewer cases in the synbiotics arm compared to fiber-free enteral nutrition (0/40 vs. 4/40) [70]. Quality of life was assessed in only one RCT using the FACT-G7 scale, and it found that reduction of quality of life was mitigated in the probiotics group [39]. This same RCT also reported FACT-G7 subscale results for fatigue, with a smaller increase in fatigue in the probiotics group [39]. One RCT reported on anthropometrics, finding mean weight loss was similar between groups (2.0 vs. 2.2 kg for synbiotics and controls) [56]. Cancer biomarker secondary outcomes were not reported.

3.10. Adverse Events in RCTs

Adverse events in RCTs are presented in detail in Table S5. Roughly half of the RCTs (17/36; 47%) did not report data about side-effects. Nine (25%) of the RCTs reported that none of the participants experienced an adverse event due to the intervention. Another 10 (28%) RCTs reported there were no severe adverse events due to the intervention, with the most common side-effects of the interventions being nausea and flatulence. One RCT reported that “we could not exclude the relationship of 2 adverse events with the test powder in the probiotics group (cholelithiasis and tremor) and 3 adverse events in the placebo group (diarrhea, tremor, and abnormal liver function)”. This trial in sigmoid colon cancer utilized Bifidobacterium animalis subsp. lactis HY8002 + Lactobacillus casei HY2782 + L. plantarum HY7712 + xylooligosaccharides + fructooligosaccharides [54]. Other postoperative complications not captured above are also presented for additional safety data (Table S5). Total noninfectious complications were in general either similar or lower in the probiotics groups. However, two (6%) RCTs found a higher rate each of pancreatic fistula (≥grade B) [68], and 30-day readmission [39], in probiotics arms.

3.11. Nonrandomized and Observational Studies

The methodological quality appraisals with the Newcastle-Ottawa Scale of the 3 nonrandomized and 3 observational cohort studies rated them as low methodological quality (Table 3). In particular, there was a lack of controlling for important potential confounding in the “comparability of cohorts on the basis of the design or analysis” item, which is a key issue for nonrandomized and observational studies. Detailed results from all six of these studies are reported in Tables S6. For the primary review outcomes, only two studies reported on mortality and one on disease progression and there was no evidence of a safety concern for these outcomes from these studies. Infections were reported in three studies, with two showing no effect and one finding more enteritis (5/75 vs. 3/81) yet fewer surgical site infections (7/75 vs. 20/81) in the probiotics group [72]. Additionally, 1 study found more patients in the probiotics group (5/23 vs. 2/22) required additional antibiotics [76]. two studies reported on length of stay, one on pain, and three on blood loss, with no evidence of a safety concern for these outcomes. Regarding adverse events and other complications not captured above, three studies did not report on adverse events [72,73,75], one found fewer complications in the probiotics group, and one found an additional serious complication (Clavien-Dindo Grade IIIb or IV) in the probiotics group (2/42 vs. 1/55) [74].
Table 3. Quality assessments of the 6 nonrandomized & observational studies.

| Author Year | Selection | Comperability | Outcome |
|-------------|-----------|---------------|---------|
| Aisu 2015 [72] | ★★★ | ★★ |         |
| Ding 2018 [73] | ★★★★★ | ★★★ |         |
| Fujio 2020 [74] | ★★★★ | ★★ |         |
| Mao 2020 [75] | ★★★★ | ★ |         |
| Mizuta 2016 [76] | ★★★★ | ★ | ★★★ |
| Rifatbegovic 2010 [77] | ★★★★ | ★ | ★★★ |

NB: More stars indicate higher quality in the Newcastle-Ottawa Scale.

4. Discussion

This large and up-to-date evidence synthesis presents the most comprehensive systematic review on this topic including 36 RCTs in 3305 participants plus six nonrandomized/observational cohort studies. Uniquely, 21 diverse probiotic formulations were evaluated across these RCTs, thereby providing a novel assessment from human controlled studies of the evidence profiles of various probiotics genera, species, strains, and combinations in this oncological surgery population. 94% of RCTs dealt with digestive system cancers, with 53% on colorectal cancer (19/36) and 22% on hepatobiliary/pancreatic cancers. 83% investigated oral products, and six RCTs administered probiotics in enteral nutrition tubes. Our findings support current thinking that probiotics effects are specific to the product/formulation. Due to substantial heterogeneity among interventions, overall conclusions regarding “probiotics” in general cannot be made, and thus we did not pool results in a meta-analysis. From our analysis, the placebo-controlled RCT identified with the most promising results overall based on direction of effect from among five trials judged as low risk-of-bias was Kotzampassi et al., 2015. This RCT in colorectal cancer included 164 total participants and gave an oral formulation of Lactobacillus acidophilus LA-5 (1.75 billion CFU) + L. plantarum (0.5 billion CFU) + Bifidobacterium lactis BB-12 (1.75 billion CFU) + Saccharomyces boulardii (1.5 billion CFU) twice a day from 1 day pre-op until 14 days post-op [43].

There was promising evidence that probiotics may have a beneficial effect on postoperative infections with 21 of 30 RCTs (70%) favoring them compared to controls based on direction of effect. In contrast, 17% (5/30) favored controls, including the Lages 2018 trial finding a postoperative infection risk of RR 1.57 (95% CI: 0.79, 3.12) with a combination of Lactobacillus acidophilus NCFM + L. rhamnosus HN001 + L. paracasei LPC-31 + Bifidobacterium lactis HN019 + fructooligosaccharides [46]. One safety concern identified in one RCT out of 11 (9%) found a greater risk of mortality (RR 3.55; 95% CI: 0.77, 16.47) in the probiotics group; however, upon inspection they did not give 11 probiotics patients (17%) antibiotic prophylaxis and later amended their protocol (whereas the initial intended comparison was probiotics vs. antibiotics). This RCT administered Lactobacillus plantarum 299v + oatmeal to patients undergoing colorectal and other abdominal surgeries [51]. This finding conflicted with 7 RCTs (64%) that favored probiotics regarding mortality. Conflicting evidence was also found for diarrhea, with three of five RCTs (60%) favoring probiotics, one showing no effect, and one favoring controls. The latter trial found an increased risk of diarrhea of RR 8.14 (95% CI: 0.45, 148.28) in colon cancer and other abdominal surgery patients administering a combination of Lactobacillus acidophilus La5 + L. bulgaricus + Bifidobacterium lactis Bb-12 + Streptococcus thermophilus + oligofructose [33].

Regarding adverse events, there wasn’t evidence of a difference in types and rates reported between groups overall. However, adverse events were poorly reported with 47% of RCTs not reporting about side-effects. A total of 25% of RCTs (9/36) reported that none of the participants experienced an adverse event due to the intervention, and 28% reported there were no severe adverse events due to the intervention. The most common side-effects of probiotics or synbiotics were nausea and flatulence. Among the six non-
randomized and observational studies, there was no evidence of a safety concern. These six studies were of low methodological quality, especially due to lack of controlling for confounding.

There was overall substantial risk-of-bias across most studies since only 14% of RCTs (5/36) were judged as low risk-of-bias in the seven elements of the Cochrane tool. In particular, there was potential selection bias and reporting bias as random sequence generation and allocation concealment were often not adequately reported, and many RCTs did not cite a trial registration record or accessible protocol.

Several related systematic reviews have been published on probiotics [11,15,78–85]. In addition to uniquely differentiating between 21 formulations, our systematic review includes more RCTs, is up to date, includes all cancer types, evaluates a broader range of outcomes, and it focuses on the oncological perioperative period. Four other systematic reviews also investigated mortality, and overall, they found no significant differences between groups [80,82,84,85]. Consistent with our findings, a beneficial effect of probiotics on preventing postop infections was found in several systematic reviews and meta-analyses in colorectal cancer patients [(odds ratio, OR 0.34; 95% CI: 0.21, 0.54) [78], (p < 0.05) [11], (OR 0.51; 95% CI: 0.38, 0.68) [79], (RR 0.72; 95% CI: 0.56, 0.92) [15], (OR 0.28; 95% CI: 0.20, 0.39) [81]], and also in non-cancer (mainly gastrointestinal) surgical populations [(RR 0.55; 95% CI: 0.39, 0.78) [83], (RR 0.48; 95% CI: 0.36, 0.63) [80], (RR 0.56; 95% CI: 0.46, 0.69) [84], (OR 0.35; 95% CI: 0.24, 0.50) [85], (RR 0.26; 95% CI: 0.08, 0.84) [82]]. Beneficial effects of probiotics on length of antibiotic therapy and/or hospital length of stay were also found in other systematic reviews [11,15,78,80,81–85]. Regarding safety, one systematic review reported that intake was well tolerated overall, and that rates of abdominal distension, cramps, and diarrhea were not significantly elevated compared to controls in the perioperative setting [84], while two reported fewer side effects from perioperative probiotics use [78,80]. Most of the systematic reviews reported substantial heterogeneity among the different probiotics ingredients evaluated; thus, conclusions on the best regimens, strains, dosages, and durations of use were not reported [11,15,78–80,81–85]. One systematic review found no significant differences in infections comparing multi-strain vs. single strain probiotics, or when preoperative administration was compared to both pre- and postoperative use [81].

This systematic review has several strengths. Protocol details were registered a priori online on the PROSPERO registry, the literature search was conducted for comprehensiveness and peer reviewed, studies were assessed for risk-of-bias, there was a broad range of outcomes evaluated, and methods and results were reported according to guidelines. The main limitations at the review-level were including only English-language reports and not searching databases from Asia (potentially adding language bias), and the direction of effect synthesis method. The main study-level limitation of the results was the majority of RCTs being judged as high/unclear risk-of-bias, which weakens the findings. Also, many studies reported adverse events inadequately. Not surprisingly, there was a high degree of heterogeneity among the 21 formulations of probiotics. Finally, some trials did not report the ‘strain’ used of the probiotics.

5. Conclusions

This large systematic review evaluated 21 diverse formulations and found encouraging results with several probiotics in this specific patient population. It also highlighted potential harms from others, thereby emphasizing the importance of not grouping all probiotics into one general category due to differing effects. Given recent developments about microbiome and the morbidity from postoperative infections, further high-quality research is warranted using those promising probiotics identified herein.
Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Supplementary Materials S1: MEDLINE Search Strategy, Table S1: Interventions/Exposures in the 6 Nonrandomized & Observational Studies, Table S2: Characteristics of the 6 Nonrandomized & Observational Studies, Figure S1: Probiotics formulations studied in more than one RCT, Tables S3: Summary Characteristics of 36 RCTs, Table S4: Additional Results from RCTs, Table S5: Adverse Events and Other Complications in 36 RCTs, Table S6: Results from Nonrandomized & Observational Studies.

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