Supplementary Materials: Metabolomics Biomarkers for Detection of Colorectal Neoplasms: A Systematic Review

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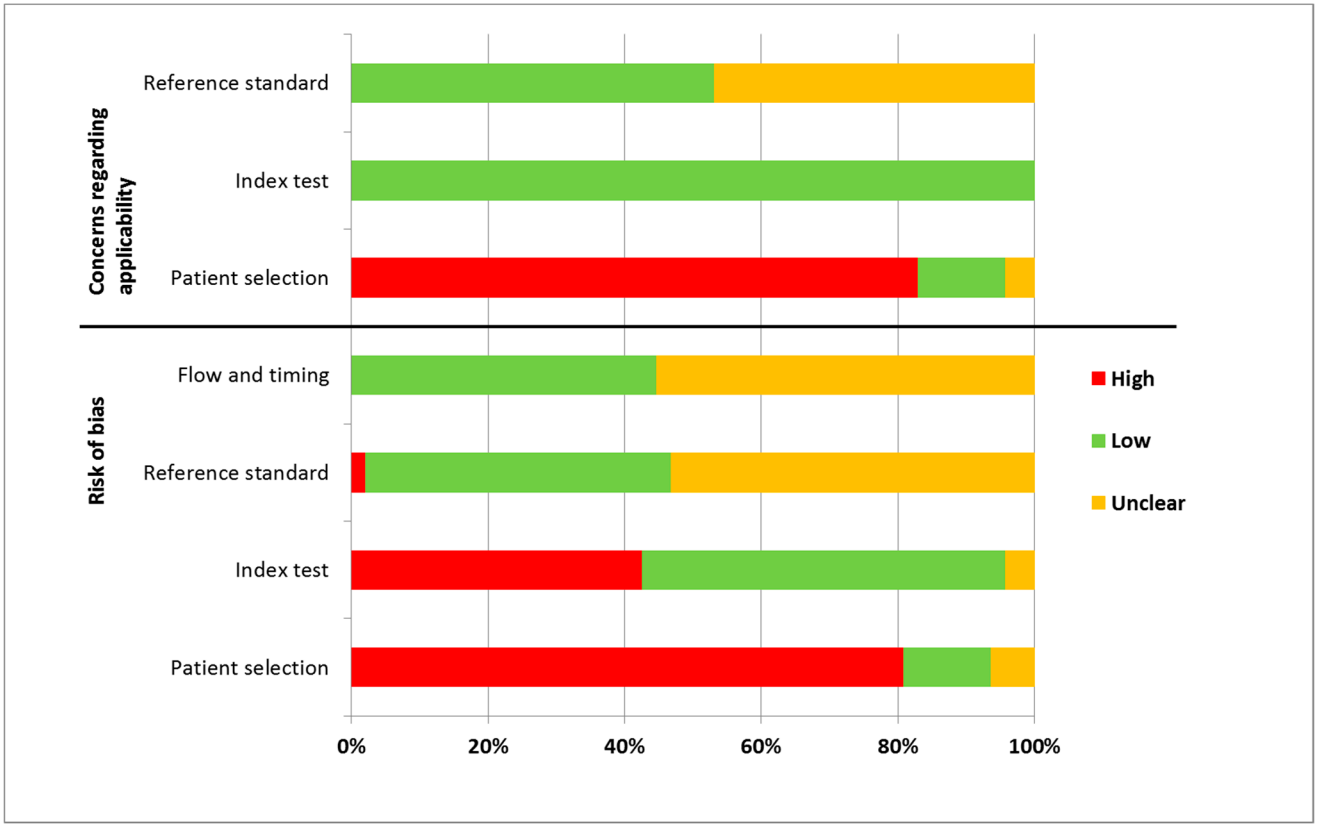
Figure S1. QUADAS Overview.



Note: red bar, proportion with high risk; green bar, proportion with low risk; yellow bar, proportion with unclear risk.

Table S1. Performance characteristics of single metabolites and metabolomic panels of potential biomarkers with additional outcomes.

First author, Year	Metabolites					Diagnostic performance							p-value
	Outcomes	Am A/ Pep	FA	CH	Others	Sn	Sp	AUC - No validation	AUC with validation				
									SS	CV	BS	EV	
Serum													
Guo, 2017 [24]	Stage I/II ♂	0	5	0	0	73.1	87.1	0.85					n.a.
	Stage I/II ♀	0	2	0	0	81.3	86.5	0.90					n.a.
Uchiyama, 2017 [23]	A	0	1 [C7]	0	0	88.0	85.0	0.92					<0.01
Farshidfar, 2016 [14]	A	2	2	1	9	n.a.	n.a.		0.81	0.81			<0.0001
Zhang, 2016 [26]	Early CRC vs. Cn + BCD	0	4	0	0	84.6	89.8		0.93				<0.001
F. Li, 2013 [29]	Stage I/II	0	10	0	0	98.1	100.0	0.99					<0.05
Nishiumi, 2012 [35]	Stage 0, I, I	3	0	1	0	82.8	n.a.		n.a.				<0.05
Plasma													
Nishiumi et al., 2017 [39]	Stage 0	3	3	2	0	100.0	100.0	n.a.					0.000781
	Stage I	3	3	2	0	97.5	91.3						
	Stage II	3	3	2	0	100.0	91.7						
S. Li, 2013 [43]	AP	0	4	0	0	89.0	80.0				n.a.		<0.05
Miyagi, 2011 [44]	Stage 0	10	0	0	0	n.a.	n.a.			0.90			<0.001
	Stage I	10	0	0	0					0.86			
	Stage II	10	0	0	0					0.92			
	Stage III	10	0	0	0					0.82			
	Stage IV	10	0	0	0					0.95			
Urine													
Nakajima, 2018 [47]	CRC vs. Cn + BCD	2	0	0	0	n.a.	n.a.				0.96		
Johnson, 2006 [20]	CRC/large P vs. small + no polyps	0	1	0	0	88.0	53.0	0.70					<0.05
Hiramatsu, 2005 [56]	Stage 0	1	0	0	0	60.0	n.a.	n.a.					<0.0001
	Stage I	1	0	0	0	62.5	n.a.						
	Stage II	1	0	0	0	71.7	n.a.						
	Stage III	1	0	0	0	83.2	n.a.						
	Stage IV	1	0	0	0	90.5	n.a.						

Abbreviations: (A)A, (advanced) adenomas; ACN, advanced colorectal neoplasms; Am A, amino acids, AP, adenomatous polyps; AUC, area under the curve; BCD, benign colorectal disease; BS, bootstrapping; C7, benzoic acid; CH, carbohydrates; CRC, colorectal cancer; CV, cross validation; EV, external validation; FA, fatty acids; P, polyps; pep, peptides; Sn, sensitivity; Sp, specificity; SS, subsampling.

Table S2. Additional potential biomarkers and biomarker panels for detection of adenomas, advanced colorectal neoplasms, polyps or early stage CRC.

Author, Year		Others
Serum		
Guo, 2017 [24]	♂Fatty acids: SM (34:1), PC (34:2), PC (34:1), PC (36:3), PC (36:2) ♀ Fatty acids: PC (36:4), PC (36:3)	
Uchiyama, 2017 [23]	Fatty acids: ↓ Benzoic acid	
Farshidfar, 2016 [14]	Amino acids/ peptides: → Cystine, Glu Fatty acids: → heptadecanoic acid, glyceric acid Carbohydrates: → erythriol	unknown (6), alkane (3)
Zhang, 2016 [26]	Fatty acids: ↓ C16:1 (palmitoleic acid), C18:2 (linoleic acid), C20:4 (arachidonic acid), C22:6 (docosahexanoic acid)	
F. Li, 2013 [29]	Fatty acids: ↓ Palmitic amide, oleamide , hexadecanedioic acid, octadecanoic acid, eicosatrienic acid, LPC(18:2), LPC(20:4), LPC(22:6), myristic acid, ↑ LPC(16:0)	
Nishiumi, 2012 [35]	Amino acids/ peptides: ↑ Asp, kynurenine, cystamine Carbohydrates: ↑ 2-hydroxybutyrate	
Plasma		
Nishiumi, 2017 [39]	Amino acids/ peptides: ↑ Orn, ↓ Trp, Lys Fatty acids: ↑ glycolic acid, ↓ palmitoleic acid, 3-hydroxyisovaleric acid Carbohydrates: ↑ Pyruvic acid, fumaric acid	
S. Li, 2013 [43]	Fatty acids: →Saturated LPC, 20:4 LPC, 16:0 sphingomyelin, 18:0 sphingomyelin	
Miyagi, 2011 [44]	Amino acids/ peptides: ↑Ser, Ala, Ile, Leu, Lys, ↓ Val, Tyr, His, Trp, Arg	
Urine		
Nakajima, 2018 [47]	Amino acids/ peptides: ↑ N1, N12-acetylspermine, N1,N8-acetylspermidine	
Johnson, 2006 [20]	Fatty acids: ↑ PGE-M	
Hiramatsu, 2005 [6]	Amino acids/ peptides: ↑ N1,N12-Diacetylspermine	

Abbreviations: Ala, alanine; Arg, arginine; His, histidine; Ile, isoleucine; Leu, leucine; LPC, lysophosphatidylcholine; Lys, lysine; Orn, ornithine; PGE-M, Prostaglandin E2 metabolite; Ser, serine, Trp, tryptophan; Tyr, tyrosine; Val, valine.

Table S3. Biochemical affiliations of potential biomarkers and biomarker panels.

First author, Year		Others
Dried blood spot		
Jing, 2017 [18]	Amino acids/ peptides: ↓ Arg, Phe/Tyr, Ala, Val Fatty acids: ↑ C16, ↓ C4/C8, C5/C3, C4/C3	
Serum		
Zhang, 2018 [22]	Fatty acids: ↑ 5-hydroxyl-eicosatetraenoic acid, ↓ 12-hydroxyl-eicosatetraenoic acid	
Guo, 2017 [24]	Fatty acids ♂: SM (34:1), PC (34:2), PC (34:1), PC (36:3), PC (36:2); Fatty acids ♀: PC (36:4), PC (36:3)	
Hata, 2017 [25]	Fatty acids: ↓ Gastrointestinal tract acid 446 (GTA-446)	
Uchiyama, 2017 [23]	Amino acids/ peptides: ↓ His; Fatty acids: ↑ Octanoic acid, decanoic acid, ↓ Benzoic acid	
Farshidfar, 2016 [14]	Amino acids/ peptides: ↑ Phe, Ile, Lys, Gly, Tyr, Ala, allo Thr, ↓ Cystine, threonic acid Fatty acids: ↑ Stearic acid, glyceric acid, palmitic acid, linoleic acid, 2-monostearoyl-glycerol, ↓ Glycerol palmitate, hexadecanoic acid derivative Carbohydrates: ↑ Lactic acid, di-TMS ethylene glycol, citric acid, myo-inositol glycerol-3-phosphate, 3-hydroxy butanoic acid, 2-hydroxy butanoic acid, ↓ Fructose, D-ribose 5-phosphate, glycerol, arabinose, malonic acid	↓ nonane, unknown (11), alkane (1)
Y. Zhang, 2016 [26]	Fatty acids: ↓ C16:1 (palmitoleic acid), C18:3 (linolenic acid), C18:2 (linoleic acid), C18:1 (oleic acid), C20:4 (arachidonic acid), C22:6 (docosahexanoic acid)	
H. Gu, 2015 [27]	Amino acids/ peptides: ↑ Asp, Glu, ↓ Gln /Lys, His, Arg, Ser, Tyr	
Zhu, 2014 [28]	Amino acids/ peptides: ↑ Hyp/ aminolevulinate, hippuric acid, leucic acid, ↓ His, 2-aminoadipate, N-acetylglycine, Met Fatty acids: ↑ Glycocholate, glycochenodeoxycholate, ↓ Linolenic acid Carbohydrates: ↑ Glyceraldehyde, maleic acid, ↓ Malonic acid/ 3-hydroxybutyrate (3HBA)	
F. Li, 2013 [29]	Fatty acids: ↑ LPC(16:0), ↓ Palmitic amide, oleamide, hexadecanedioic acid, octadecanoic acid, eicosatrienoic acid, myristic acid, LPA(16:0), LPA(18:0)	
Ritchie, 2013 [30]	Fatty acids: ↓ Gastrointestinal tract acid 446 (GTA-446)	
Tan, 2013 [31]	Amino acids/ peptides: ↓ 4-Hyp, Orn, Trp, Phe, Glu, urea Fatty acids: ↑ Oleic acid Carbohydrates: ↑ 2-hydroxybutanoic acid, 3-hydroxybutanoic acid, pyruvate	
Ikeda, 2012 [32]	Amino acids/ peptides: ↑ L-Ala, L-Gln, → L-Pro, L-Met, L-Glu, Asn Fatty acids: ↑ Glycolic acid, thiodiglycolic acid, 3-hydroxy-propionic acid Carbohydrates: ↑ Glucuronoic lactone, lactic acid, 3-hydroxy-isobutyric acid	
Leichtle, 2012 [33]	Amino acids/ peptides: ↓ Gly, Lys, Ala, Asp, His, Leu/Ile, Met, sarcosine, Thr, Tyr, Val	
Ma, 2012 [34]	Amino acids/ peptides: ↓ L-Val, L-Thr, Gly Carbohydrates: ↑ 3-hydroxybutyric acid, ↓ ribitol ↓, 1-deoxyglucose	
Nishiumi, 2012 [35]	Amino acids/ peptides: ↑ Asp, kynurenine, cystamine Carbohydrates: ↑ 2-hydroxybutyrate	

Ritchie, 2010 [36]	Fatty acids: ↓ C28H46O4 (446), C28H48O4 (448), C28H50O4 (450)
Ludwig, 2009 [37]	Fatty acids: → Acetate; Carbohydrates: → Lactate, pyruvate, 3-hydroxybutyrate, acetoacetate
Plasma	
Liu, 2018 [38]	Amino acids/ peptides: ↑ Homocysteine
Nishiumi, 2017 [39]	Amino acids/ peptides: ↑ Orn, ↓ Trp, Lys Fatty acids: ↑ Glycolic acid, ↓ Palmitoleic acid, 3-hydroxyisovaleric acid Carbohydrates: ↑ Pyruvic acid, fumaric acid
Shen, 2017 [40]	Fatty acids: ↑ PG (34:0), SM (42:2), Cer (44:5), ↓ LPC (18:3), LPC (18:2), PE (O-36:3), PE (O-38:3), SM (38:8)
Crotti, 2016 [41]	Fatty acids: ↑ Decanoic acid
Cavia-Saiz, 2014 [42]	Amino acids/ peptides: ↑ L-Kynurenine
S. Li, 2013 [43]	Fatty acids: ↓ Saturated LPC, 18:2 LPC, SPC
Miyagi, 2011 [44]	Amino acids/ peptides: ↑ Ser, Ala, Ile, Leu, Lys, ↓ Val, Tyr, His, Trp, Arg
Okamoto, 2009 [45]	Amino acids/ peptides: ↓ Thr, Val, ↑ Glu, alpha-aminobutyric acid, Gln, Pro
Zhao, 2007 [46]	Fatty acids: 18:2-LPC ,18:1 LPC, unsat. LPC, sat. LPC
Urine	
Nakajima, 2018 [47]	Amino acids/ peptides: ↑ N1,N12-Diacetylspermine
Deng, Chang, 2017 [48]	Fatty acids: ↓ Carnitine Carbohydrates: ↓ Succinic acid, ascorbic acid
Deng, Fang, 2017 [19]	Amino acids/ peptides: ↓ Ser, → β-Ala, p-Methylhistidine, Asn, trigonelline, His, Tyr Fatty acids: → Butyrate, adipate Carbohydrates: → Methanol, ethanol, 3-hydroxymandelate, benzoate, acetone, 3-Hydroxybutyrate, 3-Hydroxy-phenylacetate, 2-oxoglutarate
Wang, 2017 [49]	Amino acids/ peptides: ↓ Asn, Ala, Gln Carbohydrates: ↑ Acetoacetate
Rozalski, 2015 [50]	Carbohydrates: ↑ 8-oxo-7,8-dihydroguanine, 8-oxo-7,8-dihydro-2′-deoxyguanosine, ↓ 5-hydroxymethyluracil
Wang, 2014 [51]	Amino acids/ peptides: ↓ Ser, → β-Ala, p-Methylhistidine, Asn, trigonelline, His, Tyr Fatty acids: → Butyrate, adipate Carbohydrates: →Methanol, ethanol, 3-hydroxymandelate, benzoate, acetone, 3-Hydroxybutyrate, 3-Hydroxy-phenylacetate, 2-oxoglutarate
Eisner, 2013 [16]	Amino acids/ peptides: ↑ Trigonelline, Tyr Carbohydrates: ↓ Methanol, ↓ acetone
Hsu, 2013 [52]	Carbohydrates: ↑ Adenosine, cytidine, 3-methylcytidine, 1-methyladenosine, inosine, 2-deoxyguanosine
Yue, 2013 [17]	Fatty acids: ↓ C9H18N2O, C14H14N12O, C13H13NO4, C15H20NO5, O-octanoyl-R-carnitine, C19H35NO5, sphinganine, dihydrosphingosine, Unknown (1) 16H22O4
Chen, 2012 [53]	Amino acids/ peptides: ↑ Arg, Ile, Leu, Val, ↓ His, Met, Ser, Asp Carbohydrates: ↑ Lactic acid, ↓ Citric acid, malic acid, succinate
Cheng, 2012 [54]	Amino acids/ peptides: ↑ Putrescine, 2-aminobutyrate, ↓ Kynurenate, hippurate Fatty acids: ↑ Myristate

	Carbohydrates: ↓ Citrate, p-cresol	
Wang, 2010 [21]	Amino acids/ peptides: → Phenylacetylglutamine, leucylproline, aspartyllysine, prolylleucine Fatty acids: → Acylcarnitine (C13:0), acetylcarnitine, acylcarnitine (C9:0), acylcarnitine (C9-OH), C11H20O4N2	Unknown (3)
Wang, 2010 [21]	Carbohydrates: ↑ Pseudouridine, cytidine, 2,2-dimethylguanosine, uridine, (1 unknown), 1-methyladenosine, N6-methyladenosine	
Johnson, 2006 [20]	Fatty acids: ↑ PGE-M	
Feng, 2005 [55]	Carbohydrates: ↑ Pseudouridine, 1-methylguanosine	
Hiramatsu, 2005 [56]	Amino acids/ peptides: ↑ N1,N12-Diacetylspermine	
Zheng, 2005 [57]	Carbohydrates: ↑ Pseudouridine, cytidine, 1-methyladenosine, inosine, 5-methyluridine, 1-methylinosine, 1-methylguanosine, N4-acetylcytidine, N2-methylguanosine, adenosine, N2,N2-methylguanosine, N6-methyladenosine, ↓ uridine, guanosine	
Feces		
Lin, 2016 [58]	Amino acids/ peptides: ↓ Gln, ↑ Pro, Ile/Leu/Val, Ala, Glu, dimethylglycine Fatty acids: ↓ Acetate, propionate, butyrate Carbohydrates: ↑ Succinate, lactate, ↓ Glucose	
Amiot, 2015 [59]	Amino acids/ peptides: ↓ Gln, Glu Fatty acids: ↑ Valerate, propionate, butyrate, acetate Carbohydrates: ↓ β-glucose	
Phua, 2014 [15]	Fatty acids: ↓ Linoleic acid Carbohydrates: ↓ Nicotinic acid, fructose	
Bezabeh, 2009 [60]	Amino acids/ peptides: → Glu, Val, Ile Fatty acids: → n-butyric acid, lipid	

Abbreviations: Ala, alanine; Arg, arginine; Asn, asparagine; Asp, aspartic acid (aspartate); Cer, ceramide; Cys, cysteine, Gln, glutamine; Glu, glutamic acid (glutamate); GTA-446, Gastrointestinal tract acid 446; His, histidine; Hyp, hydroxyproline; Ile, isoleucine; Leu, leucine; LPA, lysophosphatidic acid; LPC, lysophosphatidylcholine; Lys, lysine; Met, methionine; Orn, ornithine; PC, phosphatidylcholine, PE, phosphatidylethanolamine; PG, phosphatidylglycerol; PGE-M, Prostaglandin E2 metabolite; Phe, phenylalanine; Pro, proline; sat, saturated; Ser, serine; SM, sphingomyelin; SPC, sphingosylphosphorylcholine; Thr, threonine; Trp, tryptophan; Tyr, tyrosine; unsat, unsaturated; Val, valine.

Table S4. QUADAS tool.

First author, Year	Risk of bias				Concerns regarding applicability		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Dried blood spot							
Jing, 2017 [18]	☹	☺	☺	☺	☹	☺	☺
Serum							
Zhang, 2018 [22]	☹	☹	☹	? 😐	☹	☺	? 😐
Guo, 2017 [24]	☹	☹	? 😐	? 😐	☹	☺	? 😐
Hata, 2017 [25]	☹	☹	? 😐	? 😐	☹	☺	☺
Uchiyama, 2017 [23]	☹	☹	? 😐	? 😐	☹	☺	? 😐
Farshidfar, 2016 [14]	☹	☺	☺	☺	☹	☺	☺
Y. Zhang, 2016 [26]	☹	☺	? 😐	? 😐	☹	☺	? 😐
H. Gu, 2015 [27]	☺	☺	☺	☺	☺	☺	☺
Zhu, 2014 [28]	? 😐	☺	☺	☺	? 😐	☺	☺
F. Li, 2013 [29]	☹	☹	? 😐	? 😐	☹	☺	? 😐
Ritchie, 2013 [30]	? 😐	? 😐	☺	? 😐	☹	☺	☺
Tan, 2013 [31]	☹	☺	? 😐	? 😐	☹	☺	? 😐
Ikeda, 2012 [32]	☹	☹	☺	☺	☹	☺	☺
Leichtle, 2012 [33]	☹	☺	? 😐	? 😐	☹	☺	? 😐
Ma, 2012 [34]	☹	☹	? 😐	? 😐	☹	☺	? 😐
Nishiumi, 2012 [35]	☹	☺	? 😐	☺	☹	☺	☺
Ritchie, 2010 [36]	☹	☺	☺	? 😐	☹	☺	☺
Ludwig, 2009 [37]	☹	☹	? 😐	? 😐	☹	☺	? 😐
Plasma							
Liu, 2018 [38]	☹	☹	? 😐	? 😐	☹	☺	? 😐
Nishiumi, 2017 [39]	☹	☹	☺	? 😐	☹	☺	☺
Shen, 2017 [40]	☹	☹	? 😐	? 😐	☹	☺	? 😐
Crotti, 2016 [41]	☹	☹	☺	☺	☹	☺	☺
Cavia-Saiz, 2014 [42]	☹	☹	☺	☺	☹	☺	☺
S. Li, 2013 [43]	☹	☺	☺	☺	☹	☺	☺
Miyagi, 2011 [44]	☹	☺	? 😐	? 😐	☹	☺	? 😐
Okamoto, 2009 [45]	☹	☺	? 😐	☺	☹	☺	? 😐
Zhao, 2007 [46]	☹	☺	? 😐	? 😐	☹	☺	? 😐
Urine							
Nakajima, 2018 [47]	☹	☺	? 😐	? 😐	☹	☺	? 😐
Deng, Chang, 2017 [48]	☺	☺	☺	☺	☺	☺	☺
Deng, Fang, 2017 [19]	☺	☹	☺	☺	☺	☺	☺
Wang, 2017 [49]	☹	☺	? 😐	? 😐	☹	☺	? 😐
Rozalski, 2015 [50]	☹	☹	☺	☺	☹	☺	☺
Wang, 2014 [51]	☺	☺	☺	☺	☺	☺	☺
Eisner, 2013 [16]	☺	☺	☺	☺	☺	☺	☺
Hsu, 2013 [52]	☹	☹	? 😐	? 😐	☹	☺	? 😐
Yue, 2013 [17]	☹	☺	? 😐	? 😐	☹	☺	? 😐
Chen, 2012 [53]	☹	☹	? 😐	☺	☹	☺	☺
Cheng, 2012 [54]	☹	☺	? 😐	? 😐	☹	☺	? 😐
Wang, 2010 [21]	☹	☺	? 😐	? 😐	☹	☺	? 😐
Johnson, 2006 [20]	☹	☹	☺	☺	☹	☺	☺
Feng, 2005 [55]	☹	☹	? 😐	? 😐	☹	☺	? 😐
Hiramatsu, 2005 [56]	☹	☹	? 😐	? 😐	☹	☺	? 😐
Zheng, 2005 [57]	☹	? 😐	☺	☺	☹	☺	☺
Feces							
Lin, 2016 [58]	☹	☺	☺	? 😐	☹	☺	☺
Amiot, 2015 [59]	☺	☺	☺	☺	☺	☺	☺
Phua, 2014 [15]	☹	☺	? 😐	☺	☹	☺	☺
Bezabeh, 2009 [60]	? 😐	☺	☺	☺	? 😐	☺	☺

Note: ☹ high risk; ☺ low risk; **?** 😐 unclear risk.