Role of pharmacogenomics in predicting efficacy and safety of thiopurines in inflammatory bowel disease: A systematic review and meta-analysis

APPENDIX 1

INDEX

Search strategy

Database: Ovid MEDLINE Completo - Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Search Strategy:

----

1 exp Azathioprine/

2 azathioprine.mp.

3 (((mercaptopurine or puri-nethol or purimethol or purinethol or bw 57 323h or bw 57-323h or bw 57323h) adj1 1 methyl 4 nitro 5 imidazolyl) or mercaptopurine or Arathioprin or arathioprine or aza-q or azafalkazahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or azathiopine or azathioprim or azathioprin or azathioprine sodium or azathiopurine or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or azothioprin or azathioprine or bw 57 322 or bw 57-322 or bw 57322 or bw57-322 or bw57322 or Colinsan or immuran or immurel or immuthera or imunen or imuprin or Imuran or imurane or imurek or imurel or imuren or nsc 39084 or nsc39084 or thioazeprine or Thioprine or transimune or zytrim).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

4 mercaptopurine*.mp. or exp Mercaptopurine/

5 thiopurine*.mp.

6 (6 mercapto purine or 6 mercaptopurin or 6 mercaptopurine or 6 mercaptopurine monohydrate or 6 mp or 6 purinethiol or 6 purinethiol hydrate or 6 thiohypoxanthine or 6 thiopurine or 6-mercaptopurine or classen or empurine or ismipur or leukerin or leupurin or leupurine or loulla or mercaleukin or mercaptopurin or mercaptopurina or mercapurene or mern or mycaptine or nsc 755 or nsc755 or puri nethol or puri-nethol or purine 6 thiol or purine thiol 6 or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol

supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

7 or/1-6

8 (gene* adj1 mutation*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

9 (gene* adj1 alteration*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

10 exp Mutation/ or exp Genetics/

11 polymorphism*.mp. or exp Polymorphism, Genetic/

12 exp Genotype/ or genotyp*.mp. or genogroup*.mp.

13 or/8-12

14 exp inflammatory bowel diseases/ or exp colitis, ulcerative/ or exp crohn disease/

15 ((colitis adj1 (granulomatous or enteritis)) or ((crohn or crohn's or crohns) adj1 (disease or enteritis)) or ileocolitis or ((regional or terminal) adj1 (enteritis or ileitides or ileitis))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

16 ((colitis adj1 (gravis or ulcerative)) or idiopathic proctocolitis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

17 (inflammatory enteropathy or intestinal inflammation or intestine inflammation or cleron disease or Crohn's disease or Crohns disease or enteritis regionalis or intestinal tract,regional enteritis or morbus Crohn or regional enteritis or regional enterocolitis or chronic ulcerative

colitis or colitis ulcerative or colitis ulcerosa or colitis ulcerosa chronica or colitis, ulcerative or colitis,ulcerative or colitis,ulcerous or colon,chronic ulceration or histiocytic ulcerative colitis or mucosal colitis or ulcerative colorectitis or ulcerative procto colitis or ulcerative proctocolitis or ulcerous colitis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

18 14 or 15 or 16 or 17

19 7 and 13 and 18

****

Database: Embase

Search Strategy:

----

1 exp Azathioprine/

2 azathioprine.mp.

3 (((mercaptopurine or puri-nethol or purimethol or purinethol or bw 57 323h or bw 57-323h or bw 57323h) adj1 1 methyl 4 nitro 5 imidazolyl) or mercaptopurine or Arathioprin or arathioprine or aza-q or azafalkazahexal or azamedac or azamun or azamune or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or azathiopine or azathioprim or azathioprin or azathioprine sodium or azathiopurine or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or azothioprin or azathioprine or bw 57 322 or bw 57-322 or bw 57322 or bw57-322 or bw57322 or Colinsan or immuran or immurel or immuthera or imunen or imuprin or Imuran or imurane or imurek or imurel or imuren or nsc 39084 or nsc39084 or thioazeprine or Thioprine or transimune or zytrim).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

4 exp mercaptopurine/ or mercaptopurine*.mp.

5 exp thiopurine methyltransferase/ or thiopurine*.mp.

6 (6 mercapto purine or 6 mercaptopurin or 6 mercaptopurine or 6 mercaptopurine monohydrate or 6 mp or 6 purinethiol or 6 purinethiol hydrate or 6 thiohypoxanthine or 6 thiopurine or 6-mercaptopurine or classen or empurine or ismipur or leukerin or leupurin or leupurine or loulla or mercaleukin or mercaptopurin or mercaptopurina or mercapurene or mern or mycaptine or nsc 755 or nsc755 or puri nethol or puri-nethol or purine 6 thiol or purine thiol 6 or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine or xaluprine).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

7 or/1-6

8 (gene* adj1 mutation*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

9 (gene* adj1 alteration*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

10 exp Mutation/ or exp Genetics/

11 polymorphism*.mp. or exp genetic polymorphism/

12 exp genotype/ or genotyp*.mp. or genogroup*.mp.

13 or/8-12

14 ((colitis adj1 (granulomatous or enteritis)) or ((crohn or crohn's or crohns) adj1 (disease or enteritis)) or ileocolitis or ((regional or terminal) adj1 (enteritis or ileitides or ileitis))).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

15 ((colitis adj1 (gravis or ulcerative)) or idiopathic proctocolitis).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

16 exp Crohn disease/ or exp inflammatory bowel disease/ or exp ulcerative colitis/

17 (inflammatory enteropathy or intestinal inflammation or intestine inflammation or cleron disease or Crohn's disease or Crohns disease or enteritis regionalis or intestinal tract,regional

enteritis or morbus Crohn or regional enteritis or regional enterocolitis or chronic ulcerative colitis or colitis ulcerative or colitis ulcerosa or colitis ulcerosa chronica or colitis, ulcerative or colitis,ulcerative or colitis,ulcerous or colon,chronic ulceration or histiocytic ulcerative colitis or mucosal colitis or ulcerative colorectitis or ulcerative procto colitis or ulcerative proctocolitis or ulcerous colitis).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

18 or/14-17

19 7 and 13 and 18

…………………………………..

Database: Cochrane library

Search Strategy:

ID	Search Hits
#1	MeSH descriptor: [Azathioprine] explode all trees
#2	(azathioprine):ti,ab,kw
#3	MeSH descriptor: [Mercaptopurine] explode all trees
#4	mercaptopurine
#5	thiopurine*
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	gene mutation
#8	gene alteration
#9	MeSH descriptor: [Mutation] explode all trees
#10	MeSH descriptor: [Genetics] explode all trees
#11	MeSH descriptor: [Polymorphism, Genetic] explode all trees
#12	polymorphism*
#13	MeSH descriptor: [Genotype] explode all trees
#14	genotyp*
#15	genogroup*
#16	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17	MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees
#18	MeSH descriptor: [Colitis, Ulcerative] explode all trees
#19	MeSH descriptor: [Crohn Disease] explode all trees
#20	inflammatory bowel disease
#21	ulcerative colitis
#22	Crohn disease
#23	Crohn's disease
#24	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#25	#6 AND #16 AND #24

Studies included for #Objective 2

Adam, L., Soma, P., & Phulukdaree, A. (2018). Identification of single-nucleotide polymorphisms in inflammatory bowel disease patients on azathioprine therapy. *South African Medical Journal*, *108*(8), 687. https://doi.org/http://dx.doi.org/10.7196/SAMJ.2018.v108i8.13516

Akiyama, S., Matsuoka, K., Fukuda, K., Hamada, S., Shimizu, M., Nanki, K., … Kanai, T. (2019). Long-term effect of NUDT15 R139C on hematologic indices in inflammatory bowel disease patients treated with thiopurine. *Journal of Gastroenterology and Hepatology*. https://doi.org/http://dx.doi.org/10.1111/jgh.14693

Al-Judaibi, B., Schwarz, U. I., Huda, N., Dresser, G. K., Gregor, J. C., Ponich, T., … Kim, R. B. (2016). Genetic predictors of azathioprine toxicity and clinical response in patients with inflammatory bowel disease. *Journal of Population Therapeutics and Clinical Pharmacology*, *23*(1), e26–e36.

Ansari, A., Arenas, M., Greenfield, S. M., Morris, D., Lindsay, J., Gilshenan, K., … Sanderson, J. (2008). Prospective evaluation of the pharmacogenetics of azathioprine in the treatment of inflammatory bowel disease. *Alimentary Pharmacology and Therapeutics*, *28*(8), 973–983. https://doi.org/http://dx.doi.org/10.1111/j.1365-2036.2008.03788.x

Asada, A., Nishida, A., Shioya, M., Imaeda, H., Inatomi, O., Bamba, S., … Andoh, A. (2016). NUDT15 R139C-related thiopurine leukocytopenia is mediated by 6-thioguanine nucleotide-independent mechanism in Japanese patients with inflammatory bowel disease. *Journal of Gastroenterology*, *51*(1), 22–29.

Ban, H., Andoh, A., Imaeda, H., Kobori, A., Bamba, S., Tsujikawa, T., … Fujiyama, Y. (2010). The multidrug-resistance protein 4 polymorphism is a new factor accounting for thiopurine sensitivity in Japanese patients with inflammatory bowel disease. *Journal of Gastroenterology*, *45*(10), 1014–1021.

Banerjee, R., Ravikanth, V. V., Pal, P., Bale, G., Avanthi, U. S., Goren, I., … Reddy, D. N. (2020). NUDT15 C415T variant compared with TPMT genotyping in predicting azathioprine-induced leucopenia: prospective analysis of 1014 inflammatory bowel disease patients in India. *Alimentary Pharmacology & Therapeutics*, *52*(11–12), 1683–1694. https://doi.org/https://dx.doi.org/10.1111/apt.16137

Bangma, A., Voskuil, M. D., Uniken Venema, W. T. C., Brugge, H., Hu, S., Lanting, P., … Weersma, R. K. (2020). Predicted efficacy of a pharmacogenetic passport for inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*, *51*(11), 1105–1115. https://doi.org/https://dx.doi.org/10.1111/apt.15762

Bourgine, J., Billaut-Laden, I., Colombel, J. F., & Broly, F. (2012). Evidence for a functional genetic polymorphism of the Rho-GTPase Rac1: Implication in azathioprine response? *Fundamental and Clinical Pharmacology*, *26 (SUPPL.*, 16–17. https://doi.org/http://dx.doi.org/10.1111/j.1472-8206.2012.01032.x

Chao, K., Zhu, X., Cao, Q., Yang, H., Liang, J., Lin, L., … Gao, X. (2017). Combined detection variants of NUDT15 could highly predict thiopurine-induced leukopenia in Chinese patients with inflammatory bowel disease: A multi-center analysis. *Journal of Crohn’s and Colitis*, *11 (Supple*, S125. https://doi.org/http://dx.doi.org/10.1093/ecco-jcc/jjx002.222

Choi, R., Lee, M.-N., Kim, K., Baek, S.-Y., Kim, T. J., Hong, S. N., … Lee, S.-Y. (2020). Effects of various genetic polymorphisms on thiopurine treatment-associated outcomes for Korean patients with Crohn's disease. *British Journal of Clinical Pharmacology*, *86*(11), 2302–2313. https://doi.org/https://dx.doi.org/10.1111/bcp.14339

Coelho, T., Andreoletti, G., Ashton, J. J., Batra, A., Afzal, N. A., Gao, Y., … Ennis, S. (2016). Genes implicated in thiopurine-induced toxicity: Comparing TPMT enzyme activity with clinical phenotype and exome data in a paediatric IBD cohort. *Scientific Reports*, *6*, 34658. https://doi.org/https://dx.doi.org/10.1038/srep34658

Cravo, M., Ferreira, P., Sousa, P., Moura-Santos, P., Velho, S., Tavares, L., … Brito, M. (2014). Clinical and genetic factors predicting response to therapy in patients with crohn's disease. *United European Gastroenterology Journal*, *2*(1), 47–56.

De Ridder, L., Van Dieren, J. M., Van Deventer, H. J., Stokkers, P. C., Van der Woude, J. C., Van Vuuren, A. J., … Hommes, D. W. (2006). Pharmacogenetics of thiopurine therapy in paediatric IBD patients. *Alimentary Pharmacology & Therapeutics*, *23*(8), 1137–1141.

Demlova, R., Mrkvicova, M., Sterba, J., Bernatikova, H., Stary, J., Sukova, M., … Valik, D. (2014). Augmenting clinical interpretability of thiopurine methyltransferase laboratory evaluation. *Oncology (Switzerland)*, *86*(3), 152–158.

Dubinsky, M. C., Lamothe, S., Yang, H. Y., Targan, S. R., Sinnett, D., Theoret, Y., & Seidman, E. G. (2000). Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. *Gastroenterology*, *118*(4), 705–713.

Fangbin, Z., Xiang, G., Liang, D., Hui, L., Xueding, W., Baili, C., … Pinjin, H. (2016). Prospective Evaluation of Pharmacogenomics and Metabolite Measurements upon Azathioprine Therapy in Inflammatory Bowel Disease: An Observational Study. *Medicine*, *95*(15), e3326. https://doi.org/https://dx.doi.org/10.1097/MD.0000000000003326

Franca, R., Stocco, G., Favretto, D., Giurici, N., del Rizzo, I., Locatelli, F., … Rabusin, M. (2020). PACSIN2 rs2413739 influence on thiopurine pharmacokinetics: validation studies in pediatric patients. *Pharmacogenomics Journal*, *20*(3), 415–425. https://doi.org/10.1038/s41397-019-0130-0

Gazouli, M., Pachoula, I., Panayotou, I., Mantzaris, G., Syriopoulou, V. P., Goutas, N., … Roma-Giannikou, E. (2010). Thiopurine S-methyltransferase genotype and the use of thiopurines in paediatric inflammatory bowel disease Greek patients. *Journal of Clinical Pharmacy and Therapeutics*, *35*(1), 93–97. https://doi.org/http://dx.doi.org/10.1111/j.1365-2710.2009.01041.x

Gearry, R. B., Barclay, M. L., Burt, M. J., Collett, J. A., Chapman, B. A., Roberts, R. L., & Kennedy, M. A. (2003). Thiopurine S-methyltransferase (TPMT) genotype does not predict adverse drug reactions to thiopurine drugs in patients with inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*, *18*(4), 395–400.

Giudici, F., Cavalli, T., Luceri, C., Russo, E., Zambonin, D., Scaringi, S., … Malentacchi, C. (2021). Long-Term Follow-Up, Association between CARD15/NOD2 Polymorphisms, and Clinical Disease Behavior in Crohn's Disease Surgical Patients. *Mediators of Inflammation*, *2021*, 8854916. https://doi.org/https://dx.doi.org/10.1155/2021/8854916

Grover, N., Bhatia, P., Kumar, A., Mandavdhare, H., Prasad, K., Samanta, J., … Singh, M. (2020). Genetic polymorphisms in prediction of thiopurine related cytopenia in inflammatory bowel disease: A prospective study. *Indian Journal of Gastroenterology*, *39*(SUPPL 1), S27. https://doi.org/http://dx.doi.org/10.1007/s12664-020-01133-9

Hawwa, A. F., Millership, J. S., Collier, P. S., Vandenbroeck, K., McCarthy, A., Dempsey, S., … McElnay, J. C. (2008). Pharmacogenomic studies of the anticancer and immunosuppressive thiopurines mercaptopurine and azathioprine. *British Journal of Clinical Pharmacology*, *66*(4), 517–528. https://doi.org/https://dx.doi.org/10.1111/j.1365-2125.2008.03248.x

Heap, G. A., Weedon, M. N., Bewshea, C. M., Singh, A., Chen, M., Satchwell, J. B., … Ahmad, T. (2014). HLA-DQA1–HLA-DRB1 variants confer susceptibility to pancreatitis induced by thiopurine immunosuppressants. *Nature Genetics*, *46*(10), 1131–1134. https://doi.org/10.1038/ng.3093

Hibi, T., Naganuma, M., Kitahora, T., Kinjyo, F., & Shimoyama, T. (2003). Low-dose azathioprine is effective and safe for maintenance of remission in patients with ulcerative colitis. *Journal of Gastroenterology*, *38*(8), 740–746.

Hindorf, U., Lindqvist, M., Peterson, C., Soderkvist, P., Strom, M., Hjortswang, H., … Almer, S. (2006). Pharmacogenetics during standardised initiation of thiopurine treatment in inflammatory bowel disease. *Gut*, *55*(10), 1423–1431. https://doi.org/http://dx.doi.org/10.1136/gut.2005.074930

Hlavaty, T., Batovsky, M., Balakova, D., Pav, I., Celec, P., Gregus, M., … Slovak, I. B. D. study group. (2013). The impact of thiopurine-S-methyltransferase genotype on the adverse drug reactions to azathioprine in patients with inflammatory bowel diseases. *Bratislavske Lekarske Listy*, *114*(4), 199–205.

Kakuta, Y., Kawai, Y., Okamoto, D., Takagawa, T., Ikeya, K., Sakuraba, H., … Suzuki, Y. (2018). NUDT15 codon 139 is the best pharmacogenetic marker for predicting thiopurine-induced severe adverse events in Japanese patients with inflammatory bowel disease: a multicenter study. *Journal of Gastroenterology*, *53*(9), 1065–1078. https://doi.org/http://dx.doi.org/10.1007/s00535-018-1486-7

Kakuta, Y., Naito, T., Onodera, M., Kuroha, M., Kimura, T., Shiga, H., … Shimosegawa, T. (2016). NUDT15 R139C causes thiopurine-induced early severe hair loss and leukopenia in Japanese patients with IBD. *Pharmacogenomics Journal*, *16*(3), 280–285.

Kang, B., Kim, T. J., Choi, J., Baek, S.-Y., Ahn, S., Choi, R., … Choe, Y. H. (2020). Adjustment of azathioprine dose should be based on a lower 6-TGN target level to avoid leucopenia in NUDT15 intermediate metabolisers. *Alimentary Pharmacology & Therapeutics*, *52*(3), 459–470. https://doi.org/https://dx.doi.org/10.1111/apt.15810

Kim, H. S., Cheon, J. H., Jung, E. S., Park, J., Aum, S., Park, S. J., … Lee, M. G. (2017). A coding variant in FTO confers susceptibility to thiopurine-induced leukopenia in East Asian patients with IBD. *Gut*, *66*(11), 1926–1935.

Kim, J. H., Cheon, J. H., Hong, S. S., Eun, C. S., Byeon, J. S., Hong, S. Y., … Kim, W. H. (2010). Influences of thiopurine methyltransferase genotype and activity on thiopurine-induced leukopenia in Korean patients with inflammatory bowel disease: a retrospective cohort study. *Journal of Clinical Gastroenterology*, *44*(10), e242-8. https://doi.org/https://dx.doi.org/10.1097/MCG.0b013e3181d6baf5

Kim, M. J., Lee, S. Y., & Choe, Y. H. (2014). Monitoring thiopurine metabolites in Korean pediatric patients with inflammatory bowel disease. *Yonsei Medical Journal*, *55*(5), 1289–1296. https://doi.org/http://dx.doi.org/10.3349/ymj.2014.55.5.1289

Koifman, E., Karban, A., Mazor, Y., Chermesh, I., Waterman, M., Almog, R., … Chowers, Y. (2013). Thiopurine effectiveness in patients with Crohn's disease: A study of genetic and clinical predictive factors. *Inflammatory Bowel Diseases*, *19*(8), 1639–1644.

Larussa, T., Suraci, E., Lentini, M., Nazionale, I., Gallo, L., Abenavoli, L., … Luzza, F. (2012). High prevalence of polymorphism and low activity of thiopurine methyltransferase in patients with inflammatory bowel disease. *European Journal of Internal Medicine*, *23*(3), 273–277. https://doi.org/https://dx.doi.org/10.1016/j.ejim.2011.12.002

Lee, J. H., Kim, T. J., Kim, E. R., Hong, S. N., Chang, D. K., Choi, L. H., … Kim, Y. H. (2017). Measurements of 6-thioguanine nucleotide levels with TPMT and NUDT15 genotyping in patients with Crohn's disease. *PLoS ONE [Electronic Resource]*, *12*(12), e0188925. https://doi.org/https://dx.doi.org/10.1371/journal.pone.0188925

Lee, M., Kang, B., Woo, S. Y., Kim, J., Lee, S., & Choe, Y. H. (2015). Impact of genetic polymorphisms on 6-thioguanine nucleotide levels and toxicity in pediatric IBD patients treated with azathioprine. *Clinical Chemistry and Laboratory Medicine*, *1)*, S781.

Liu, Q., Wang, Y., Mei, Q., Han, W., Hu, J., & Hu, N. (2016). Measurement of red blood cell 6-thioguanine nucleotide is beneficial in azathioprine maintenance therapy of Chinese Crohn's disease patients. *Scandinavian Journal of Gastroenterology*, *51*(9), 1093–1099. https://doi.org/http://dx.doi.org/10.3109/00365521.2016.1161068

Lucafo, M., Stocco, G., Martelossi, S., Favretto, D., Franca, R., Malusa, N., … Decorti, G. (2019). Azathioprine Biotransformation in Young Patients with Inflammatory Bowel Disease: Contribution of Glutathione-S Transferase M1 and A1 Variants. *Genes*, *10 (4) (no*(277). https://doi.org/http://dx.doi.org/10.3390/genes10040277

Maeda, T., Sakuraba, H., Hiraga, H., Yoshida, S., Kakuta, Y., Kikuchi, H., … Fukuda, S. (2021). Long-term efficacy and tolerability of dose-adjusted thiopurine treatment in maintaining remission in inflammatory bowel disease patients with NUDT15 heterozygosity. *Intestinal Research*. https://doi.org/https://dx.doi.org/10.5217/ir.2020.00133

Mahasneh, S., Sharab, A., Al Shhab, M., Rashid, M., & Zihlif, M. (2020). AOX1 and XDH Enzymes Genotyping and its Effect on Clinical Response to Azathioprine in Inflammatory Bowel Disease Patients Among Jordanian Population. *Current Drug Metabolism*, *21*(2), 140–144. https://doi.org/https://dx.doi.org/10.2174/1389200221666200413125011

Marinaki, A. M., Ansari, A., Duley, J. A., Arenas, M., Sumi, S., Lewis, C. M., … Sanderson, J. D. (2004). Adverse drug reactions to azathioprine therapy are associated with polymorphism in the gene encoding inosine triphosphate pyrophosphatase (ITPase). *Pharmacogenetics*, *14*(3), 181–187.

Mazor, Y., Koifman, E., Elkin, H., Chowers, Y., Krivoy, N., Karban, A., & Efrati, E. (2013). Risk factors for serious adverse effects of thiopurines in patients with Crohn's disease. *Current Drug Safety*, *8*(3), 181–185.

Mendoza, J. L., Urcelay, E., Lana, R., Martin, M. C., Lopez, N., Guijarro, L. G., … Diaz-Rubio, M. (2007). MDR1 polymorphisms and response to azathioprine therapy in patients with Crohn's disease. *Inflammatory Bowel Diseases*, *13*(5), 585–590. https://doi.org/http://dx.doi.org/10.1002/ibd.20044

Mhanna, M., Gharaibeh, M. G., Rashid, M., Sharab, A., Shehab, M., & Zihlif, M. (2019). TPMT Genotype and Adverse Effects of Azathioprine among Jordanian Group. *Current Drug Metabolism*, *20*(11), 889–897. https://doi.org/https://dx.doi.org/10.2174/1389200220666191021100953

Naughton, M. A., Battaglia, E., O'Brien, S., Walport, M. J., & Botto, M. (1999). Identification of thiopurine methyltransferase (TPMT) polymorphisms cannot predict myelosuppression in systemic lupus erythematosus patients taking azathioprine. *Rheumatology*, *38*(7), 640–644.

Niess, J. H., Klaus, J., Stephani, J., Pfluger, C., Degenkolb, N., Spaniol, U., … von Boyen, G. B. (2012). NOD2 polymorphism predicts response to treatment in Crohn's disease--first steps to a personalized therapy. *Digestive Diseases & Sciences*, *57*(4), 879–886. https://doi.org/https://dx.doi.org/10.1007/s10620-011-1977-3

Odahara, S., Uchiyama, K., Kubota, T., Ito, Z., Takami, S., Kobayashi, H., … Ohkusa, T. (2015). A Prospective Study Evaluating Metabolic Capacity of Thiopurine and Associated Adverse Reactions in Japanese Patients with Inflammatory Bowel Disease (IBD). *PLoS ONE [Electronic Resource]*, *10*(9), e0137798. https://doi.org/https://dx.doi.org/10.1371/journal.pone.0137798

Palmieri, O., Latiano, A., Bossa, F., Vecchi, M., D'Inca, R., Guagnozzi, D., … Annese, V. (2007). Sequential evaluation of thiopurine methyltransferase, inosine triphosphate pyrophosphatase, and HPRT1 genes polymorphisms to explain thiopurines' toxicity and efficacy. *Alimentary Pharmacology and Therapeutics*, *26*(5), 737–745. https://doi.org/http://dx.doi.org/10.1111/j.1365-2036.2007.03421.x

Park, S. K., Hong, M., Ye, B. D., Kim, K. J., Park, S. H., Yang, D. H., … Yang, S. K. (2016). Influences of XDH genotype by gene-gene interactions with SUCLA2 for thiopurine-induced leukopenia in Korean patients with Crohn's disease. *Scandinavian Journal of Gastroenterology*, *51*(6), 684–691.

Reuther, L. O., Sonne, J., Larsen, N. E., Larsen, B., Christensen, S., Rasmussen, S. N., … Schmiegelow, K. (2003). Pharmacological monitoring of azathioprine therapy. *Scandinavian Journal of Gastroenterology*, *38*(9), 972–977.

Ribaldone, D. G., Adriani, A., Caviglia, G. P., Nicolo, A., Agnesod, D., Simiele, M., … Astegiano, M. (2019). Correlation between Thiopurine S-Methyltransferase Genotype and Adverse Events in Inflammatory Bowel Disease Patients. *Medicina*, *55*(8), 5. https://doi.org/https://dx.doi.org/10.3390/medicina55080441

Schwab, M., Schaffeler, E., Marx, C., Fischer, C., Lang, T., Behrens, C., … Kaskas, B. A. (2002). Azathioprine therapy and adverse drug reactions in patients with inflammatory bowel disease: Impact of thiopurine S-methyltransferase polymorphism. *Pharmacogenetics*, *12*(6), 429–436. https://doi.org/http://dx.doi.org/10.1097/00008571-200208000-00003

Shah, S. A. V, Paradkar, M., Desai, D., & Ashavaid, T. F. (2017). Nucleoside diphosphate-linked moiety X-type motif 15 C415T variant as a predictor for thiopurine-induced toxicity in Indian patients. *Journal of Gastroenterology and Hepatology (Australia)*, *32*(3), 620–624. https://doi.org/http://dx.doi.org/10.1111/jgh.13494

Smith, M. A., Marinaki, A. M., Arenas, M., Shobowale-Bakre, M., Lewis, C. M., Ansari, A., … Sanderson, J. D. (2009). Novel pharmacogenetic markers for treatment outcome in azathioprine-treated inflammatory bowel disease. *Alimentary Pharmacology and*

Therapeutics, *30*(4), 375–384. https://doi.org/http://dx.doi.org/10.1111/j.1365-2036.2009.04057.x

Steponaitiene, R., Kupcinskas, J., Survilaite, S., Varkalaite, G., Jonaitis, L., Kiudelis, G., … Kupcinskas, L. (2016). TPMT and ITPA genetic variants in Lithuanian inflammatory bowel disease patients: Prevalence and azathioprine-related side effects. *Advances in Medical Sciences*, *61*(1), 135–140.

Stocco, G., Martelossi, S., Barabino, A., Decorti, G., Bartoli, F., Montico, M., … Ventura, A. (2007). Glutathione-S-transferase genotypes and the adverse effects of azathioprine in young patients with inflammatory bowel disease. *Inflammatory Bowel Diseases*, *13*(1), 57–64. https://doi.org/http://dx.doi.org/10.1002/ibd.20004

Stocco, G., Martelossi, S., Barabino, A., Fontana, M., Lionetti, P., Decorti, G., … Ventura, A. (2005). TPMT genotype and the use of thiopurines in paediatric inflammatory bowel disease. *Digestive and Liver Disease*, *37*(12), 940–945. https://doi.org/http://dx.doi.org/10.1016/j.dld.2005.08.003

Stocco, G., Martelossi, S., Decorti, G., Ventura, A., Malusa, N., Bartoli, F., & Giraldi, T. (2004). Pharmacogenetics of thiopurines: Can posology be guided by laboratory data? *Radiology and Oncology*, *38*(2), 101-109+157.

Stocco, G., Martelossi, S., Sartor, F., Toffoli, G., Lionetti, P., Barabino, A., … Ventura, A. (2006). Prevalence of methylenetetrahydrofolate reductase polymorphisms in young patients with inflammatory bowel disease. *Digestive Diseases & Sciences*, *51*(3), 474–479.

Sutiman, N., Chen, S., Ling, K. L., Chuah, S. W., Leong, W. F., Nadiger, V., … Chowbay, B. (2018). Predictive role of NUDT15 variants on thiopurine-induced myelotoxicity in Asian inflammatory bowel disease patients. *Pharmacogenomics*, *19*(1), 31–43. https://doi.org/https://dx.doi.org/10.2217/pgs-2017-0147

Takatsu, N., Matsui, T., Murakami, Y., Ishihara, H., Hisabe, T., Nagahama, T., … Yao, K. (2009). Adverse reactions to azathioprine cannot be predicted by thiopurine S-methyltransferase genotype in Japanese patients with inflammatory bowel disease. *Journal of Gastroenterology & Hepatology*, *24*(7), 1258–1264. https://doi.org/https://dx.doi.org/10.1111/j.1440-1746.2009.05917.x

van Dieren, J. M., van Vuuren, A. J., Kusters, J. G., Nieuwenhuis, E. E., Kuipers, E. J., & van der Woude, C. J. (2005). ITPA genotyping is not predictive for the development of side effects in AZA treated inflammatory bowel disease patients. *Gut*, *54*(11), 1664.

Von Ahsen, N., Armstrong, V. W., Behrens, C., Von Tirpitz, C., Stallmach, A., Herfarth, H., … Reinshagen, M. (2005). Association of inosine triphosphatase 94C>A and thiopurine S-methyltransferase deficiency with adverse events and study drop-outs under azathioprine therapy in a prospective Crohn disease study. *Clinical Chemistry*, *51*(12), 2282–2288. https://doi.org/http://dx.doi.org/10.1373/clinchem.2005.057158

Wang, H. H., He, Y., Wang, H. X., Liao, C. L., Peng, Y., Tao, L. J., … Yang, H. X. (2018). Comparison of TPMT and NUDT15 polymorphisms in Chinese patients with inflammatory bowel disease. *World Journal of Gastroenterology*, *24*(8), 941–948. https://doi.org/https://dx.doi.org/10.3748/wjg.v24.i8.941

Weiss, B., Lebowitz, O., Fidder, H. H., Maza, I., Levine, A., Shaoul, R., … Karban, A. (2010). Response to medical treatment in patients with Crohn's disease: the role of

NOD2/CRAD15, disease phenotype, and age of diagnosis. *Digestive Diseases & Sciences*, *55*(6), 1674–1680. https://doi.org/https://dx.doi.org/10.1007/s10620-009-0936-8

Wilson, A., Jansen, L. E., Rose, R. V, Gregor, J. C., Ponich, T., Chande, N., … Kim, R. B. (2018). HLA-DQA1-HLA-DRB1 polymorphism is a major predictor of azathioprine-induced pancreatitis in patients with inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*, *47*(5), 615–620. https://doi.org/https://dx.doi.org/10.1111/apt.14483

Winter, J. W., Gaffney, D., Shapiro, D., Spooner, R. J., Marinaki, A. M., Sanderson, J. D., & Mills, P. R. (2007). Assessment of thiopurine methyltransferase enzyme activity is superior to genotype in predicting myelosuppression following azathioprine therapy in patients with inflammatory bowel disease. *Alimentary Pharmacology & Therapeutics*, *25*(9), 1069–1077.

Wroblova, K., Kolorz, M., Batovsky, M., Zboril, V., Suchankova, J., Bartos, M., … Bartosova, L. (2012). Gene polymorphisms involved in manifestation of leucopenia, digestive intolerance, and pancreatitis in azathioprine-treated patients. *Digestive Diseases & Sciences*, *57*(9), 2394–2401. https://doi.org/https://dx.doi.org/10.1007/s10620-012-2163-y

Xu, Y., Qiao, Y.-Q., Li, H.-Y., Zhou, M., Cai, C.-W., Shen, J., & Ran, Z.-H. (2020). NUDT15 genotyping during azathioprine treatment in patients with inflammatory bowel disease: Implications for a dose-optimization strategy. *Gastroenterology Report*, *8*(6), 437–444. https://doi.org/http://dx.doi.org/10.1093/gastro/goaa021

Yang, S. K., Hong, M., Baek, J., Choi, H., Zhao, W., Jung, Y., … Song, K. (2014). A common missense variant in NUDT15 confers susceptibility to thiopurine-induced leukopenia. *Nature Genetics*, *46*(9), 1017–1020. https://doi.org/http://dx.doi.org/10.1038/ng.3060

Zabala-Fernandez, W., Barreiro-de Acosta, M., Echarri, A., Carpio, D., Lorenzo, A., Castro, J., … Barros, F. (2011). A pharmacogenetics study of TPMT and ITPA genes detects a relationship with side effects and clinical response in patients with inflammatory bowel disease receiving Azathioprine. *Journal of Gastrointestinal & Liver Diseases*, *20*(3), 247–253.

Zabala, W., Cruz, R., Acosta, M. B., Chaparro, M., Panes, J., Echarri, A., … Barros, F. (2015). Exome-wide pharmacogenomic analysis of response to thiopurines in inflammatory bowel disease patients. *Current Pharmacogenomics and Personalized Medicine*, *13*(1), 61–67. https://doi.org/http://dx.doi.org/10.2174/1875692113666150813151413

Zabala, W., Cruz, R., Barreiro-de Acosta, M., Chaparro, M., Panes, J., Echarri, A., … investigators, E. (2013). New genetic associations in thiopurine-related bone marrow toxicity among inflammatory bowel disease patients. *Pharmacogenomics*, *14*(6), 631–640. https://doi.org/https://dx.doi.org/10.2217/pgs.13.38

Zelinkova, Z., Derijks, L. J., Stokkers, P. C., Vogels, E. W., van Kampen, A. H., Curvers, W. L., … Hommes, D. W. (2006). Inosine triphosphate pyrophosphatase and thiopurine s-methyltransferase genotypes relationship to azathioprine-induced myelosuppression. *Clinical Gastroenterology & Hepatology*, *4*(1), 44–49.

Tables

Table S1. Study characteristics (objective 1)

Author, year	Design	Unit of allocation	Center	Location	Study period	Arms	Analysis	Population of interest, no.	Baseline imbalances	Withdrawals, exclusions	Age, years	Sex, males, no. (%)	Race, no. (%)	Crohn Disease, no. (%)	Children, no. (%)	Analyzed genes	Thiopurine doses
Chang 2020	RCT	Individual	MC	Korea	01/2016-09/2018	2	ITT	182	Yes	Genotyping +: 15 exclusions, 9 loss to follow-up; genotyping -: 3 exclusions, 4 loss to follow-up	Genotyping +: 39.7±15.9; genotyping -: 37.7±17.1	98 (59.8%)	100% Asian	85 (51.8 %)	0	*TPMT, NUDT15, FTO*	Control: start with AZA 50 mg/day and increasing Heterozygous: 50 mg/
Chao 2021	RCT	Individual	MC	China	August 2016-November 2017	2	ITT	442	Yes	Intervention: 6 lost to follow-up Control: 13 lost to follow-up	Intervention: 26 (21-33) Control: 26 (22-31)	Intervention: 150 (68.5%) Control: 164 (80.4%)	100% Chinese Han	442 (100%)	Unknown (Inclusion criteria 14-75 years)	*NUDT15*	Control: AZA 2 mg/kg/day Heterozygous: 50% of the dose
Coenen 2015	RCT	Groups of 4	MC	The Netherlands	Recruitment: 10/2007-12/2010	2	ITT	783	Yes	13	40.5 (SD: 15.8)	354 (45.2%)	NR	476 (60.8 %)	0	*TPMT*	Control: AZA 2-2.5 mg/kg/day Heterozygous: 50% of the dose
Newman 2011	RCT	Individual	MC	UK	10/2005-12/2007	2	ITT	333	No	6	NR overall	165 (49.5%)	White: 303 (90.1%); Asian: 20 (6.0%); Black: 6 (1.85), Other: 4 (1.25)	140 (42.0 %)	333 (100%) ≥16 years	*TPMT*	Wild type: AZA 1.5-3 mg/kg/day Heterozygous: start with 25-50 mg/day and increasing
Wilson 2020	Historically controlled study	Individual	UC	Canada	03/2017 (control: 2012)-02/2020 (control: 2017)	2	NA	972	No	0	Genotyping +: 42.4 (18-86); genotyping -: 41.3 (18-79)	Genotyping +: 150 (45.7%); genotyping -: 170 (45.6%)	NR	458 (65.3 %)	972 (100%) > 17 years	*HLA DQA1-HLADRB 1*07:01 A.C*	No information

AZA: azathioprine; ITT: intention to treat; MC: multicenter; NA: not applicable; NR: not reported; RCT: randomized controlled trial; SD: standard deviation

Table S2. Study characteristics (objective 2)

Author, year	Design	Center	Location	Study period	Population of interest	Baseline imbalances by genotype	Withdrawals, exclusions	Age, years	Sex, males, no. (%)	Race, no. (%)	Crohn Disease, no. (%)	Ulcerative colitis, no. (%)	Children, no. (%)	Population of interest is a subgroup of all study participants	Analyzed genes
Adam 2018	C	MC	South Africa	NR	40	NR	NR	NR	13 (33%)	Black: 4 (10%); White: 32 (80%); Coloured: 1 (2.5%); Indian: 3 (7.5%)	NR	NR	NR	Yes	*TPMT*
Akiyama 2019	C	MC	Japan	11/2014-12/2015	83	No	17	35.1 (SD: 11.7)	47 (56.6%)	Japanese: 83 (100%)	54 (65.1%)	29 (34.9%)	0	No	*TPMT, NUDT15*
Al-Judaibi 2016	C	UC	Canada	2005-2010	53	NR	4	41 (Min: 19; Max: 80)	32 (60.4%)	Caucasian: 48 (90.6%); Other: 5 (9.4%)	35 (66.0%)	18 (34.0%)	0	No	*TPMT, ITPA94, GSTP 313, GSTM1, GSTT1*
Ansari 2008	C	MC	UK, Australia	NR	207	NR	8	40.3 (range: 18-80)	100 (48.3%)	NR	117 (56.5%)	90 (43.5%)	0	No	*TPMT, ITPA*
Asada 2016	C	UC	Japan	Recruitment: 05/2015-07/2015	161	NR	NR	UC: 37.0±1.4; CD: 32.3±1.2	97 (60.2%)	Japanese: 161 (100%)	72 (44.7%)	89 (55.3%)	NR	Yes	*TPMT, NUDT15, ITPA, MRP4*
Ban 2010	C	UC	Japan	NR	130	NR	4	Total trial population: 40.8 (range: 13-81)	Total trial population: 173 (62.0%)	Japanese: 130 (100%)	55 (42.3%)	75 (57.7%)	Some children. NR	Yes	*TPMT, ITPA, MRP4*
Banerjee 2020	C	UC	India	NR	1014	No	79	35.84±12.74	565 (60.4%)	Indian: 1014 (100%)	413 (40.7%)	506 (49.9%)	0	No	*NUDT15*

Bangma 2020	C	UC	The Netherlands	01/1981-12/2018	695	NR	NR	47 (IQR: 23)	286 (41.2%)	The Netherlands: 695 (100%)	404 (58.1%)	267 (38.4%)	NR	Yes	*TPMT, NUDT15, HLA-DQA1*02:01-HLA-DRB1*07:01* (rs2647087)*, HLA-DQA1*05* (rs2097432)
Bourgine 2011	C	UC	France	NR	128	NR	NR	NR	66 (51.6%)	Caucasian: 128 (100%)	103 (80.5%)	25 (19.5%)	0	Yes	*TPMT, Rac1*
Chao 2017	C	MC	China	07/2012-11/2015	732	Yes	0	28 (4-68)	507 (69.3%)	Chinese Han: 732 (100%)	660 (90.2%)	60 (8.2%)	Some children. NR	No	*TPMT, NUDT15*
Choi 2020	C	UC	Korea	01/2014-03/2015	131	NR	NR	33.0 (IQR: 26.3-40.0)	107 (81.7%)	Korean: 131 (100%)	131 (100%)	0	0	No	*TPMT, NUDT15, ITPA,* other 34 genes
Coelho 2016	C	UC	UK	NR	78	NR	NR	NR	41 (53%)	Predominantly Caucasian	49 (63%)	17 (22%)	78 (100%)	Yes	*TPMT*
Cravo 2014	C	MC	Portugal	NR	160	NR	NR	Total trial population: 39 (SD: 12.8)	Total trial population: 109 (45%)	NR	160 (100%)	0	NR	Yes	*ABCB1, IL23R, CASP9, Fas, FasL, ATG16L1*
Demlova 2014	C	MC	Czech Republic, Bratislava	01/2009. End NR	16	No	NR	NR	9 (56.3%)	NR	NR	NR	0	Yes	*TPMT*
De Ridder 2006	C	MC	The Netherlands	11/2003-04/2005	72	NR	0	12.5 (6.5-17.5)	38 (52.8%)	Caucasian: 60 (83.3%); Black: 9 (12.55); Asian: 3 (4.2%)	57 (79.2%)	15 (20.8%)	72 (100%)	No	*TPMT, ITPA*

Dubinsky 2000	C	UC	Canada	Recruitment: 1995-1998	92	NR	1	11.5 (range: 1-18)	41 (44.6%)	NR	79 (85.9%)	8 (8.7%)	92 (100%)	No	*TPMT*
Fangbin 2016	C	UC	China	08/2006-08/2014	132	NR	NR	34 (18-72)	76 (57.6%)	Chinese: 132 (100%)	102 (77.3%)	30 (22.7%)	0	No	*TPMT*
Franca 2020	C	MC	Italy	NR	119	NR	7	15.1 (12.3-16.9)	62 (52.1%)	White: 119 (100%)	67 (52.1%)	51 (42.9%)	119 (100%)	Yes	*TPMT, PACSIN2*
Gazouli 2010	C	UC	Greece	02/2007-08/2008	97	NR	NR	11.25 (range: 3–16)	40 (41.2%)	NR	69 (71.1%)	17 (17.5%)	97 (100%)	No	*TPMT*
Gearry 2003	CC	MC	New Zealand	01/1996-12/2002	100	NR	6	Cases: 40.6 (range: 17-74)	27 (48.2%)	Caucasian: 100 (100%)	39 (67.0%)	NR	Some children. NR	No	*TPMT*
Grover 2020	C	UC	India	01/2019-03/2020	119	No	15	36.8 (SD: 13.5)	61 (51.3%)	Indian: 119 (100%)	14 (11.8%)	105 (88.2%)	119 (100%) >12 years	No	*TPMT, NUDT15*
Giudici 2021	C	UC	Italy	01/2010-12/2014	101	Yes	NR	Total trial population: At onset: 27 (IQR: 21.5-38.5)	Total trial population: 110 (58%)	Caucasian: 101 (100%)	101 (100%)	0	0	Yes	*CARD/NOD2*
Hawwa 2008	C	MC	UK	NR	35	NR	NR	39 (15-73)	16 (46%)	NR	NR	NR	Some children of ≥15 years. NR	Yes	*TPMT, ITPA, XO*
Heap 2014	CC	MC	International.	03/2012-12/2013	2207	NR overall	NR	NR	NR	NR	NR	NR	NR	No	*TPMT, ITPA, HLA*
Hibi 2003	C	UC	Japan	1985-1999	82	NR	59	NR	NR	Japanese: 82 (100%)	35 (42.7%)	47 (57.3%)	NR	No	*TPMT*
Hindorf 2006	C	MC	Sweden	Recruitment: 01/2002-10/2003	60	NR	6	NR	32 (53.3%)	NR	33 (55%)	27 (45%)	0	No	*TPMT, ITPA*

Hlavaty 2013	C	MC	Slovakia	01/2009-05/2009	220	NR	NR	37.1 (12.4)	119 (54%)	NR	NR	NR	NR	No	*TPMT*
Kakuta 2018	CC	MC	Japan	12/2015-09/2017	1291	NR	NR	41.0 (3.84)	819 (63.4%)	Japanese: 1291 (100%)	548 (42.4%)	722 (55.9%)	Some children. NR	Yes	*NUDT15*
Kakuta 2016	C	UC	Japan	04/2002-09/2004	135	No	7	Mean (SD): 35.3 (12.2)	98 (72.6%)	Japanese: 135 (100%)	111 (82.0%)	23 (17.0%)	0	No	*NUDT15*
Kang 2020	C	UC	Korea	01/2006-08/2016	192	No	14	At AZA start: patients with leucopenia: Median 14.9 (IQR 12.8-16.5); patients without leucopenia: 14.9 (IQR 13.0-16.1)	118 (70.7%)	Korean: 192 (100%)	134 (80.2%)	33 (19.8%)	192 (100%)	No	*TPMT, NUDT15*
Kim 2017	C	MC	South Korea, Japan	07/1998-09/2015	331	NR	NR	NR	NR	East Asian: 331 (100%)	161 (48.6%)	107 (32.3%)	Some children. NR	Yes	*TPMT, NUDT15*
Kim 2014	C	UC	South Korea	03/2004-10/2011	109	NR	NR	15.8 (range 3-21)	75 (68.8%)	Korean: 109 (100%)	87 (79.8%)	22 (20.2%)	Some children. NR	No	*TPMT*
Kim 2010	C	MC	South Korea	06/1996-09/2006	286	Yes	NR	25.7 (9.3%)	187 (65.4%)	Korean: 286 (100%)	228 (79.7%)	34 (11.9%)	NR	No	*TPMT, ITPA*
Koifman 2013	C	UC	Israel	01/2000-January 2011	156	NR	27	Mean: 22.8 (SD: 10.1). Range: 5-58. Median: 20.0	84 (53.8%)	Jewish: 148 (94.8%)	156 (100%)	0	Some children. NR	No	*Rac1, Fas ligand, Caspase-9*

Larussa 2012	C	UC	Italy	NR	27	NR	NR	NR	NR	Caucasian: 27 (100%)	NR	NR	0	Yes	*TPMT*
Lee 2017	C	UC	South Korea	01/2014-03/2015	140	NR	NR	33.6 (8.8)	114 (81.4%)	NR	140 (100%)	NR	0	No	*TPMT, NUDT15*
Lee 2015	C	UC	South Korea	NR	132	NR	NR	17 (IQR: 15-18)	95 (72.0%)	Asian: 132 (100%)	99 (75.0%)	33 (25.0%)	132 (100%) <19 years	No	*TPMT*
Liu 2015	C	UC	China	NR	112	NR	0	32±15.6.Range: 18-63	71 (63.4%)	Asian: 112 (100%)	87 (77.7%)	25 (22.3)	0	No	*GSTM1, GSTT1, GSTP1, GSTA1*
Lucafò 2019	C	UC	Italy	03/2004-02/2015	111	NR	NR	NR	59 (53.2%)	Caucasian: 111 (100%)	61 (55.0%)	50 (45.0%)	Some children. NR	No	*TPMT*
Maeda 2021	C	UC	Japan	01/2015-10/2018	210	Yes	72	UC: median 43 (IQR: 30-59); CD: 38 (IQR: 26-45)	135 (64.3%)	Japanese: 210 (1005)	170 (51.0%)	103 (49.0%)	0	No	*NUDT15*
Mahasneh 2020	C	UC	Jordan	NR	100	NR	NR	Range: 17-72	50 (50%)	Jordan: 100 (100%)	NR	NR	100 (100%) ≥17 years	No	*AOX1, XDH*
Marinaki 2004	CC	UC	UK	NR	130	NR	NR	Range: 12-82	54 (41.5%)	Caucasian: 130 (100%)	100 (76.9%)	28 (21.5%)	Some children. NR	No	*TPMT, ITPA*
Mazor Y 2013	C	UC	Israel	01/2000-01/2011	176	No	0	28.8 (SD: 12.2) Range: 10-61	99 (56%)	Jewish descent: 167 (94.8%); Arab muslims: 6 (3.2%); Arab Christians: 2 (1%); Druze: 2 (1%)	176 (100%)	NR	24 (14%) <17 years	No	*TPMT, GSTM1, GSTT1*
Mendoza 2007	C	UC	Spain	NR	76	NR	36	Total trial population: At diagnosis: median: 27;	36 (47.4%)	White: 76 (100%)	76 (100%)	0	Some children. NR	Yes	*ABCB1*

								mean: 33; range: 8-80							
Mhanna 2019	C	UC	Jordan	09/2015-09/2016	149	NR	NR	39.9±15.2	67 (45.0%)	Jordanian: 149 (100%)	77 (51.7%)	65 (43.6%)	0	No	*TPMT*
Naughton MA 1999	C	UC	UK	1992-1997	15	NR	0	NR	NR	NR	NR	NR	NR	No	*TPMT*
Niess 2012	C	NR	Germany	NR	68	NR	NR	Total trial population: At diagnosis: NOD2-/-: median: 30.1 (14-59); NOD2+/-: median: 26.4 (15-48); NOD2+/+: 18	Total trial population: 77 (41.6%)	NR	68 (100%)	0	Some children. NR	Yes	*NOD2*
Odahara S 2015	C	UC	Japan	03/2008-06/2011	48	NR	2	34.2 ± 13.6	29 (60.4%)	Japanese: 48 (100%)	19 (39.6%)	29 (60.4%)	NR	No	*TPMT, ITPA*
Palmieri 2007	C	MC	Italy	NR	422 (*ITPA*: 408)	NR	0	35±14 (CD); 43.5±15 (UC)	227 (53.8%)	Caucasian: 422 (100%)	250 (59.2%)	172 (40.8%)	NR	No	*TPMT, ITPA, HPRT1*
Park 2016	C	UC	Korea	06/1989-07/2012	964	NR	950 patients XDH Genotype (p.Gly172Arg) available. 940 patients XDH Genotype (p.Asn1109T	With early leukopenia: 27 (12-46); late leukopenia: 25 (15-74); without leukopenia: 24 (13-64)	693 (71.9%)	Koreans: 964 (100%)	964 (100%)	0	Some children. NR	No	*XDH*

							hr) data available								
Reuther 2003	C	MC	Denmark	NR	71	NR	5	Median: 35 (range: 19-75)	29 (48.8%)	White: 71 (100%)	71 (100%)	0	0	No	*TPMT*
Ribaldone 2019	C	UC	Italy	06/2015-01/2016	200	NR	472 excluded	UC: 33 (13-59); CD: 30.5 (16-67)	116 (58%)	White: 200 (100%)	120 (60%)	80 (40%)	Some children. NR	No	*TPMT*
Schwab 2002	C	UC	Germany	06/2015-01/2016	93	NR	NR	UC: 42 (24-60); CD: 40 (19-71)	45 (48.4%)	Caucasian: 93 (100%)	77 (82.8%)	16 (17.2%)	0	No	*TPMT*
Smith 2009	C	MC	Uk and Australia	NR	192	NR	23	Mean: 39 (range: 16-84)	80 (41.7%)	Caucian: 178 (92.7%); Other: 14 (2.8%)	105 (54.7%)	86 (44.8%)	Some children. NR	No	*XDH, MOCOS, AOX1*
Steponaitiene 2016	C	MC	Lithuania	2011-2014	82	NR	NR	37.1 (SD: 10.1)	42 (51.2%)	White: 82 (100%)	39 (47.6%)	43 (52.4%)	0	Yes	*TPMT, ITPA*
Stocco 2007	C	MC	Italy	NR	70	NR	NR	Median: 16.17 (range: 1.61-44.66)	34 (49%)	NR	41 (59%)	29 (41%)	Some children. NR	No	*TPMT, GST P*
Stocco 2006	C	MC	Italy	06/2002-06/2004	67	NR	NR	Total trial population: Median: 15 (range: 4–38)	Total trial population: 43 (46.7%)	NR	NR	NR	Some children. NR	Yes	*MTHFR*
Stocco 2005	C	MC	Italy	07/2002-03/2004	70	NR	0	Mean: 14.2 (range: 0.8-38.8)	34 (48.6%)	NR	38 (54.3%)	31 (44.3%)	Some children. NR	No	*TPMT*

Stocco 2004	C	UC	Italy	07/2002-07/2003	44	NR	0	Mean: 16.4 (range: 4-38)	24 (54.5%)	NR	NR	NR	Some children. NR	No	*TPMT*
Sutiman 2018	C	UC	Singapur	NR	129	NR	0	42 (range: 17-18)	87 (67.4%)	Asian: 129 (100%)	89 (69.0%)	40 (31.0%)	Some children. NR	No	*TPMT, NUDT15*
Takatsu 2009	C	UC	Japan	2000	117	NR	NR	NR	NR	Japanese: 117 (100%)	71 (60.7%)	44 (37.6%)	NR	No	*TPMT*
VanDieren 2005	C	UC	The Netherlands	01/2003. End NR	109	NR	NR	NR	NR	NR	NR	NR	NR	No	*TPMT, ITPA*
von Ahsen 2005	C	MC	Germany	2000-2002	71	NR	13	Mean: 36 (SD: 11,6)	31 (43.7%)	Caucasian: 71 (100%)	71 (100%)	0	0	No	*TPMT, ITPA*
Wang 2018	C	UC	China	02/2016-11/2017	80	No	NR	33.18 (SD: 11,31)	48 (60%)	Chinese: 80 (100%)	NR	NR	Some children. NR	Yes	*TPMT, NUDT15*
Weiss 2010	C	MC	Israel	1998-2005	148	NR	There were some. NR	Total trial population: 31.5 (SD: 14.7)	Total trial population: 118 (59.3%)	NR	148 (100%)	0	NR	Yes	*NOD2/CARD15*
Wilson 2018	C	UC	Canada	07/2012-03/2017	373	No	NR	Aza-induced pancreatitis: mean: 46.15 (SD: 11.87); controls: mean: 41.25 (SD: 15.98)	170 (45.6%)	NR	245 (65.68%)	128 (34.31%)	0	No	*HLA*
Winter 2007	C	UC	UK	02/2003-07/2006	130	NR	15	Mean: 45	70 (53.8%)	NR	69 (53.1%)	61 (46.9%)	NR	No	*TPMT*

Wroblova 2012	C	MC	Czech Republic and Slovak republic	NR	188	NR	NR	37.3 (20-71)	107 (56.9%)	Caucasian: 188 (100%)	137 (72.9%)	41 (21.8%)	0	No	*TPMT, ITPA, XDH*
Xu 2020	C	UC	China	08/2016-01/2017	159	Yes	5	32 (IQR: 27-40)	113 (71.1%)	Chinese Han: 159 (100%)	131 (82.4%)	24 (15.1%)	0	No	*NUDT15*
Yang 2014	C	UC	Korea	Recruitment: 06/1989-07/2012	978	NR	213	NR	704 (72.0%)	Korean: 978 (100%)	978 (100%)	0	Some children. NR	No	*TPMT, NUDT15*
Zabala 2015	CC	MC	Spain	NR	Initial C: 167; Replication C: 90	NR	NR	Initial C: 31 (8–65); replication C 44 (19–75)	Initial C: 82 (49.1%). Replication C: 39 (43.3%)	NR	Initial C 103 (61.7%). Replication C 55 (61.1%)	Initial C 64 (38.3%). Replication C 35 (38.9%)	Some children. NR	No	*TPMT, SNX9, OR13D1, SLAC2-B, ENSG00000197176, CNGB1, STAB2, NUPL2, PION, OR13C5, APOL5, NAV1, HLA-DPB2, CSTL1, ZNF291, ZNF336, DDX27, OR10T1P, ZNF673 (FLJ20344), LRRC34*
Zabala 2013	C	MC	Spain	07/2003-10/2009	260	NR	NR	Initial C: 39 (8-69), replication: 34 (9-78)	Initial C: 84 (48.6%), replication C: 42 (48.3%)	NR	initial C: 107 (61.8%), replication C: 60 (69.0%)	initial C: 66 (38.2%), replication C: 27 (31.0%)	Some children. NR	No	*TPMT, cSNPs* related to *ADH4* gene
Zabala-Fernández 2011	CC	MC	Spain	NR	232	NR	NR	32.6 (range 8-70)	115 (49.6%)	NR	156 (67.2%)	76 (32.8%)	Some children. NR	No	*TPMT, ITPA*

Zelinkova 2006	C	UC	The Netherlands	10/1995-09/2003	262	NR	NR	Mean: 39 (17-87)	103 (39.3%)	NR	195 (74.4%)	67 (25.6%)	0	No	*TPMT, ITPA*
Zhu 2019	C	UC	China	07/2014-02/2017	411	NR	0	Median: 28 (range: 12-70)	305 (74.0%)	NR	411 (100%)	0	Some children. NR	No	*TPMT, NUDT15*

C: cohort study; CC: Case-Control study; MC: multicenter; UC: unicenter; NR: not reported

Table S3. Risk of bias (RoB2) of randomized controlled trials (objective 1)

	Randomization process	Deviations form intended interventions	Missing outcome data	Measurement of the outcome	Reported results	Overall
Chang 2020	Low	Low	Low	Low	Unclear	Unclear
Chao 2021	Low	Low	Low	Low	Low	Low
Coenen 2015	Low	Unclear	Low	Low	Low	Unclear
Newman 2011	Low	Low	Unclear	Low	Low	Unclear

Table S4. Risk of Bias assessment (ROBINS-I) of non-randomized studies (objective 1)

	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Wilson 2020	Moderate	Low	Low	Low	Low	Low	Low	Moderate

Table S5. Risk of bias (Newcastle-Ottawa Scale) of non-randomized studies (objective 2)

Cohort studies	SELECTION				COMPARABILITY	OUTCOMES			
	1	2	3	4	1	1	2	3	TOTAL SCORE
Author, year									
Adam 2018	*	*	*	*		*	*	*	7/9
Akiyama 2019	*	*	*	*		*	*	*	7/9
Al-Judaibi 2016	*	*	*				*	*	5/9
Ansari 2008	*	*	*			*	*	*	6/9
Asada 2016	*	*	*		**	*		*	7/9
Ban 2010	*	*							2/9
Banerjee 2020	*	*	*	*	**	*	*	*	9/9
Bangma 2020	*	*	*		**	*		*	7/9

Bourgine 2011			*					*	2/9
Chao 2017	*	*	*			*		*	5/9
Choi 2020	*	*	*		**	*	*		7/9
Coelho 2016	*	*	*				*	*	5/9
Cravo 2014	*	*	*	*	**	*	*	*	9/9
Demlova 2014	*	*	*						3/9
De Ridder 2006	*	*	*			*	*	*	6/9
Dubinsky 2000	*	*	*	*		*	*	*	7/9
Fangbin 2016	*	*	*	*		*		*	6/9
Fangbin 2012	*	*	*				*		4/9
Franca 2020	*	*	*			*	*	*	6/9
Gazouli 2010	*	*	*			*	*	*	6/9
Giudici 2021	*	*	*	*			*		5/9
Grover 2020	*	*	*		**	*	*	*	8/9
Hawwa 2008	*	*	*	*			*		5/9
Hibi 2003	*	*	*				*		4/9
Hindorf 2006	*	*	*		**	*	*	*	8/9
Hlavaty 2013	*	*	*			*	*	*	6/9
Kakuta 2016		*	*	*		*	*	*	6/9
Kang 2020	*	*	*	*	**	*		*	8/9
Kim 2017	*	*	*			*	*		5/9
Kim 2014	*	*	*			*		*	5/9
Kim 2010	*	*	*	*			*	*	6/9
Koifman 2013	*	*	*	*	**	*	*	*	9/9
Larussa 2012	*	*	*	*		*		*	6/9
Lee 2017	*	*	*	*		*	*	*	7/9
Lee 2015	*	*	*	*	**	*		*	8/9
Liu 2015	*	*	*		**	*	*	*	8/9

Lucafò 2019	*	*	*			*	*	*	6/9
Maeda 2021	*	*	*			*		*	5/9
Mahasneh 2020	*	*	*	*		*			5/9
Mazor 2013	*	*	*			*	*	*	6/9
Mendoza 2007	*	*	*	*		*	*	*	7/9
Mhanna 2019	*	*	*						3/9
Naughton 1999	*	*	*						3/9
Niess 2012			*	*		*	*	*	5/9
Odahara S 2015	*	*	*	*			*	*	6/9
Palmieri 2007	*	*	*	*		*	*	*	7/9
Park 2016	*	*	*			*	*	*	6/9
Reuther 2003	*	*	*	*				*	5/9
Ribaldone 2019	*	*	*	*		*	*	*	7/9
Schwab 2002	*	*	*			*		*	5/9
Smith 2009	*	*	*			*	*	*	6/9
Steponaitiene 2016	*	*	*			*	*	*	6/9
Stocco 2007	*	*	*		**	*	*	*	8/9
Stocco 2006	*	*	*				*	*	5/9
Stocco 2005	*	*	*			*	*	*	6/9
Stocco 2004	*	*	*				*	*	5/9
Sutiman 2018	*	*	*	*			*	*	6/9
Takatsu 2009	*	*	*					*	4/9
VanDieren 2005	*	*	*	*			*	*	6/9
von Ahsen 2005	*	*	*	*		*		*	6/9
Wang 2018	*	*	*		**		*	*	7/9
Weiss 2010	*	*	*	*		*	*		6/9
Wilson 2018	*	*	*			*	*	*	6/9
Winter 2007	*	*	*	*		*		*	6/9

Wroblova 2012	*	*	*			*	*	*	6/9
Xu 2020	*	*	*	*	**	*	*	*	9/9
Yang 2014	*	*	*	*		*	*		6/9
Zabala 2013	*	*	*	*	**	*	*	*	9/9
Zelinkova 2006	*	*	*	*		*	*	*	7/9
Zhu 2019	*	*	*			*	*	*	6/9
	SELECTION				**COMPARABILITY**	**EXPOSURE**			
Case-control studies	**1**	**2**	**3**	**4**	**1**	**1**	**2**	**3**	**TOTAL SCORE**
Author, year									
Gearry 2003		*	*	*		*	*		5/9
Heap 2014	*	*	*	*	**	*	*		8/9
Kakuta 2018		*		*	*	*	*	*	6/9
Marinaki 2004		*	*	*		*	*		5/9
Zabala 2015	*	*	*	*		*	*	*	7/9
Zabala-Fernández 2011		*	*	*		*	*		5/9

Table S6. Additional results for different comparisons of *TPMT* genotype for outcomes of interest

		TPMT gen		*TPMT**2			*TPMT**3		
Outcome	**No. mutated alleles vs wild-type**	**1**	**2**	**1**	**2**	**1-2**	**1**	**2**	**1-2**
All-cause mortality	**No. studies**	0	0	0	0	0	0	0	0
Total SAE	**No. studies**	12	6	1	2	2	6	3	6
	OR (95%CI)	**2.02 (1.05-3.88)**	**74.09 (12.25-448.24)**	5776 (0.00-1.7e+11)	13.02 (0.97-174.12)	**25.19 (2.71-234.18)**	2.53 (0.59-10.04)	**75.73 (5.29-1083.88)**	**5.74 (1.99-16.61)**
	I^2	1%	0%	NA	0%	27%	0%	0%	0%
	Figure	S37	S45	-	S56	S59	S66	S74	S81
Total hematologic AE	**No. studies**	38	12	5	2	6	28	8	28
	OR (95%CI)	**2.65 (2.05-3.43)**	**33.02 (9.65-112.96)**	3.54 (0.63-19.86)	8.00 (0.54-119.34)	**4.33 (1.01-18.55)**	**2.65 (1.94-3.62)**	**94.98 (14.35-628.79)**	**3.01 (2.23-4.05)**
	I^2	48%	0%	0%	0%	0%	49%	0%	53%
	Figure	S38	S46	S52	S57	S60	S67	S75	S82
Serious hematologic AE	**No. studies**	11	6	1	2	2	6	2	6
	OR (95%CI)	**4.58 (1.93-10.87)**	**79.02 (14.31-436.34)**	5776 (0.00-1.7e+11)	**26.58 (1.53-462.41)**	**51.29 (4.14-635.21)**	2.63 (0.61-11.33)	9741.13 (0.12-8.2e+08)	**5.91 (2.00-17.46)**
	I^2	0%	0%	NA	0%	14%	0%	0%	0%
	Figure	S39	S47	-	S58	S61	S68	S76	S83
Withdrawal due to AE	**No. studies**	11	4	1	1	2	5	2	5
	OR (95%CI)	**3.21 (1.91-5.41)**	**6.36 (1.28-31.48)**	0.01 (0.00-3.0e+06)	132.37 (0.01-2.5e+06)	1.39 (0.15-12.79)	**3.71 (1.91-7.22)**	1.18 (0.08-17.79)	**3.49 (1.83-6.64)**
	I^2	0%	0%	NA	NA	5%	7%	0%	10%
	Figure	S40	S48	-	-	S62	S69	S77	S84
Pancreatitis	**No. studies**	21	8	4	1	5	15	6	15
	OR (95%CI)	0.89 (0.47-1.67)	0.22 (0.00-23.55)	0.09 (0.00-226.28)	0.47 (0.00-9346.89)	0.13 (0.00-57.63)	0.72 (0.28-1.86)	0.15 (0.00-108.55)	0.67 (0.26-1.72)
	I^2	0%	0%	0%	NA	0%	0%	0%	0%
	Figure	S41	S49	S53	-	S63	S70	S78	S85
Hepatotoxicity	**No. studies**	21	8	4	1	5	16	6	17
	OR (95%CI)	0.68 (0.31-1.48)	1.57 (0.21-12.06)	0.11 (0.00-382.50)	293.09 (0.01-5.8e+06)	2.02 (0.25-16.21)	0.78 (0.35-1.75)	0.16 (0.00-105.21)	0.88 (0.44-1.79)
	I^2	0%	0%	0%	NA	0%	0%	0%	0%
	Figure	S42	S50	S54	-	S64	S71	S79	S86
Gastrointestinal AE	**No. studies**	14	7	2	0	2	12	6	12
	OR (95%CI)	**1.76 (1.02-3.03)**	0.11 (0.00-190.39)	0.09 (0.00-42594.45)	-	0.09 (0.00-42594.45)	**1.94 (1.10-3.42)**	0.10 (0.00-352.47)	**1.82 (1.04-3.20)**
	I^2	0%	0%	0%	-	0%	0%	0%	0%
	Figure	S43	S51	S55	-	S65	S72	S80	S87
Change in disease activity	**No. studies**	0	0	0	0	0	0	0	0
Clinical Remission	**No. studies**	8	1	1	0	1	5	1	5
	OR (95%CI)	1.57 (0.92-2.69)	0.00 (0.00-8.9e+08)	0.37 (0.03-4.12)	-	0.37 (0.03-4.12)	1.47 (0.75-2.86)	0.00 (0.00-8.9e+08)	1.25 (0.66-2.35)
	I^2	29%	NA	NA	-	NA	37%	NA	45%
	Figure	S44	-	-	-	-	S73	-	S88

AE: adverse events; CI: confidence interval; NA: not applicable; OR: odds ratio; SAE: serious adverse events

Table S7. Sensitivity analyses excluding studies with high risk of bias				
Outcome	**No. mutated alleles vs wild-type**	***TPMT* gen**	***ITPA* gen**	***NUDT15* gen**
All-cause mortality	**No. studies**	0	0	0
Total SAE	**No. studies**	9	1	5
	OR (95%CI)	**5.91 (2.87-12.19)**	0.30 (0.00-127.69)	**11.44 (7.36-17.77)**
	I^2	10%	NA	0%
	Figure	S89	-	S221
Total hematologic AE	**No. studies**	38	7	15
	OR (95%CI)	**3.03 (2.36-3.88)**	0.87 (0.59-1.26)	**8.36 (5.71-12.23)**
	I^2	48%	42%	80%
	Figure	S90	S155	S222
Serious hematologic AE	**No. studies**	10	1	6
	OR (95%CI)	**8.76 (4.21-18.26)**	0.30 (0.00-127.69)	**12.83 (8.21-20.04)**
	I^2	0%	NA	0%
	Figure	S91	-	S223
Withdrawal due to AE	**No. studies**	11	3	1
	OR (95%CI)	**3.28 (2.04-5.27)**	1.11 (0.48-2.55)	2.08 (0.76-5.68)
	I^2	0%	27%	NA
	Figure	S92	S156	-
Pancreatitis	**No. studies**	21	4	4
	OR (95%CI)	0.92 (0.48-1.79)	0.70 (0.22-2.17)	0.28 (0.08-1.05)
	I^2	0%	0%	0%
	Figure	S93	S157	S224
Hepatotoxicity	**No. studies**	22	5	3
	OR (95%CI)	0.73 (0.37-1.46)	0.72 (0.20-2.57)	0.63 (0.32-1.25)
	I^2	0%	0%	0%
	Figure	S94	S158	S225
Gastrointestinal AE	**No. studies**	14	2	3
	OR (95%CI)	0.80 (0.40-1.59)	0.09 (0.00-4.12)	**2.04 (1.34-3.08)**
	I^2	8%	0%	0%
	Figure	S95	S159	S226
Change in disease activity	**No. studies**	0	0	0
Clinical Remission	**No. studies**	7	2	1
	OR (95%CI)	1.28 (0.76-2.17)	0.70 (0.40-1.21)	1.07 (0.47-2.46)
	I^2	35%	0%	NA
	Figure	S96	S160	-

AE: adverse events; CI: confidence interval; NA: not applicable; OR: odds ratio; SAE: serious adverse events

Table S8. Additional results for different comparisons of *ITPA* genotype for outcomes of interest

		ITPA gen		*ITPA* 94C>A			*ITPA* IVS2 + 21A>C		
Outcome	**No. mutated alleles vs wild-type**	**1**	**2**	**1**	**2**	**1-2**	**1**	**2**	**1-2**
All-cause mortality	**No. studies**	0	0	0	0	0	0	0	0
Total SAE	**No. studies**	1	0	1	0	1	0	0	0
	OR (95%CI)	0.30 (0.00-127.69)		0.30 (0.00-127.69)		0.30 (0.00-127.69)			
	I^2	NA		NA		NA			
	Figure	-		-		-			
Total hematologic AE	**No. studies**	6	4	9	4	11	5	5	6
	OR (95%CI)	1.00 (0.59-1.69)	**0.30 (0.10-0.87)**	1.35 (0.80-2.28)	0.20 (0.00-439.41)	1.09 (0.75-1.59)	0.69 (0.33-1.46)	0.96 (0.21-4.34)	0.76 (0.40-1.44)
	I^2	44%	0%	14%	0%	15%	0%	0%	0%
	Figure	S117	S123	S126	S132	S135	S142	S146	S150
Serious hematologic AE	**No. studies**	1	0	1	0	2	0	0	0
	OR (95%CI)	0.30 (0.00-127.69)		0.30 (0.00-127.69)		1.11 (0.13-9.60)			
	I^2	NA		NA		0%			
	Figure	-		-		S136			
Withdrawal due to AE	**No. studies**	2	1	2	1	3	1	1	2
	OR (95%CI)	0.82 (0.23-2.86)	0.07 (0.00-62.86)	1.00 (0.22-4.55)	0.07 (0.00-6878.45)	1.91 (0.73-4.95)	0.50 (0.06-4.36)	0.07 (0.00-3.8e+05)	0.69 (0.21-2.23)
	I^2	13%	NA	0%	NA	21%	NA	NA	0%
	Figure	S118	-	S127	-	S137	-	-	S151
Pancreatitis	**No. studies**	4	2	7	2	8	4	4	5
	OR (95%CI)	0.74 (0.24-2.34)	0.16 (0.00-138.00)	0.92 (0.40-2.14)	0.16 (0.00-9613.47)	0.86 (0.38-1.98)	1.40 (0.63-3.11)	0.15 (0.00-45.64)	1.37 (0.64-2.93)
	I^2	0%	0%	14%	0%	7%	0%	0%	0%
	Figure	S119	S124	S128	S133	S138	S143	S147	S152
Hepatotoxicity	**No. studies**	5	2	8	2	10	4	4	5
	OR (95%CI)	0.73 (0.20-2.61)	0.73 (0.00-715.62)	1.19 (0.48-2.95)	0.52 (0.00-31889.34)	0.84 (0.35-1.99)	0.37 (0.07-2.10)	0.21 (0.00-55.25)	0.54 (0.14-2.03)
	I^2	0%	0%	0%	0%	0%	0%	0%	0%
	Figure	S120	S125	S129	S134	S139	S144	S148	S153
Gastrointestinal AE	**No. studies**	2	1	5	1	6	3	3	4
	OR (95%CI)	0.09 (0.00-4.19)	0.10 (0.00-6.3e+14)	0.72 (0.26-1.99)	0.10 (0.00-6.3e+14)	1.14 (0.50-2.57)	1.18 (0.50-2.83)	1.14 (0.15-8.51)	1.23 (0.56-2.70)
	I^2	0%	NA	34%	NA	33%	0%	8%	0%
	Figure	S121	-	S130	-	S140	S145	S149	S154
Change in disease activity	**No. studies**	0	0	0	0	0	0	0	0
Clinical Remission	**No. studies**	2	1	3	1	3	1	1	1
	OR (95%CI)	0.68 (0.39-1.19)	111.03 (0.00-7.2e+17)	0.66 (0.41-1.05)	111.03 (0.00-7.2e+17)	0.67 (0.42-1.06)	0.83 (0.47-1.46)	0.70 (0.10-5.09)	0.82 (0.47-1.43)
	I^2	0%	NA	0%	NA	0%	NA	NA	NA
	Figure	S122	-	S131	-	S141	-	-	-

AE: adverse events; CI: confidence interval; NA: not applicable; OR: odds ratio; SAE: serious adverse events

Table S9. Additional results for different comparisons of *NUDT15* genotype for outcomes of interest

		NUDT15 gen		*NUDT15* R139C		
Outcome	**No. mutated alleles vs wild-type**	**1**	**2**	**1**	**2**	**1-2**
All-cause mortality	**No. studies**	0	0	0	0	0
Total SAE	**No. studies**	5	3	4	3	4
	OR (95%CI)	**6.13 (3.76-9.98)**	**155.17 (73.19-328.96)**	**7.28 (2.92-18.15)**	**77.68 (13.58-444.29)**	**9.79 (4.12-23.24)**
	I^2	0%	43%	14%	3%	5%
	Figure	S177	S184	S190	S197	S200
Total hematologic AE	**No. studies**	15	11	11	8	12
	OR (95%CI)	**5.83 (4.22-8.06)**	**159.26 (66.44-381.74)**	**6.80 (4.46-10.38)**	**200.91 (45.09-895.18)**	**6.83 (4.25-10.98)**
	I^2	72%	0%	70%	0%	78%
	Figure	S178	S185	S191	S198	S201
Serious hematologic AE	**No. studies**	6	4	6	4	6
	OR (95%CI)	**6.89 (4.24-11.22)**	**173.77 (83.18-363.03)**	**5.66 (2.58-12.37)**	**152.29 (32.10-722.51)**	**9.79 (4.71-20.35)**
	I^2	22%	28%	0%	25%	0%
	Figure	S179	S186	S192	S199	S202
Withdrawal due to AE	**No. studies**	2	1	2	1	1
	OR (95%CI)	1.93 (0.89-4.20)	**26.73 (4.40-162.43)**	**3.12 (1.40-6.97)**	**26.73 (4.40-162.43)**	2.08 (0.76-5.68)
	I^2	55%	NA	0%	NA	NA
	Figure	S180	-	S193	-	-
Pancreatitis	**No. studies**	4	2	2	1	2
	OR (95%CI)	0.32 (0.09-1.18)	0.08 (0.00-64.64)	0.29 (0.01-11.79)	0.32 (0.00-9953.97)	0.27 (0.01-5.69)
	I^2	0%	0%	0%	NA	0%
	Figure	S181	S187	S194	-	S203
Hepatotoxicity	**No. studies**	3	2	2	1	2
	OR (95%CI)	0.66 (0.32-1.34)	0.48 (0.07-3.41)	0.41 (0.06-2.68)	0.19 (0.00-5720.91)	0.39 (0.06-2.54)
	I^2	0%	0%	0%	NA	0%
	Figure	S182	S188	S195	-	S204
Gastrointestinal AE	**No. studies**	3	2	2	1	2
	OR (95%CI)	**1.96 (1.26-3.04)**	**2.52 (1.10-5.81)**	1.02 (0.21-4.97)	6.12 (0.60-62.55)	1.40 (0.36-5.55)
	I^2	0%	0%	0%	NA	0%
	Figure	S183	S189	S196	-	S205
Change in disease activity	**No. studies**	0	0	0	0	0
Clinical Remission	**No. studies**	1	0	1	0	1
	OR (95%CI)	1.07 (0.47-2.46)	-	1.07 (0.47-2.46)	-	1.07 (0.47-2.46)
	I^2	NA	-	NA	-	NA
	Figure	-	-	-	-	-

AE: adverse events; CI: confidence interval; NA: not applicable; OR: odds ratio; SAE: serious adverse events

Table S10. Additional results for different comparisons of *NUDT15* genotype for outcomes of interest

		NUDT15*2			***NUDT15*3***			***NUDT15*4***			***NUDT15*5***			***NUDT15*6***		
Outcome	**No. mutated alleles vs wild-type**	**1**	**2**	**1-2**	**1**	**2**	**1-2**	**1**	**2**	**1-2**	**1**	**2**	**1-2**	**1**	**2**	**1-2**
Total SAE	**No. studies**	**1**	1	1	1	1	1	1	1	1	2	1	2	0	0	0
	OR (95%CI)	6.43 (2.54-16.26)	513.75 (107.05-1465.46)	20.33 (9.84-41.99)	8.38 (3.86-18.19)	171.12 (66.50-441.02)	20.80 (10.65-40.61)	0.07 (0.00-2.6e+07)	36946.44 (0.00-3.1e+20)	16.31 (3.06-86.80)	2.59 (0.33-20.17)	3.00 (0.37-24.30)	2.28 (0.29-17.68)	-	-	-
	I^2	NA	NA	NA	NA	NA	NA	NA	NA	NA	0%	NA	0%	-	-	-
	Figure	-	-	-	-	-	-	-	-	-	S212	-	S216	-	-	-
Total hematologic AE	**No. studies**	2	2	2	3	3	3	1	1	1	4	2	4	2	1	2
	OR (95%CI)	5.57 (3.80-8.17)	222.34 (28.38-1741.81)	7.96 (5.59-11.34)	3.41 (2.51-4.65)	143.64 (42.04-490.73)	5.45 (4.12-7.20)	1.47 (0.17-12.38)	6096.05 (0.00-5.1e+19)	4.41 (1.08-18.01)	2.51 (1.18-5.31)	5.21 (2.18-12.45)	3.55 (1.85-6.80)	3.45 (1.39-6.82)	2932 (0.00-9.8e+22)	3.89 (1.91-9.41)
	I^2	0%	0%	0%	0%	0%	0%	NA	NA	NA	0%	32%	0%	0%	NA	0%
	Figure	S206	S207	S208	S209	S210	S211	-	-	1	S213	S215	S217	S219	-	S220
Serious hematologic AE	**No. studies**	1	1	1	1	1	1	1	1	1	2	1	2	0	0	0
	OR (95%CI)	6.43 (2.564-16.26)	20.33 (9.84-41.99)	20.33 (9.84-41.99)	8.38 (3.86-18.19)	171.25 (66.50-441.02)	20.80 (10.65-40.61)	0.07 (0.00-2.6e+07)	36946.44 (0.00-3.1e+20)	16.31 (3.06-86.80)	2.59 (0.33-20.17)	3.00 (0.37-24.30)	2.28 (0.29-17.68)	-	-	-
	I^2	NA	NA	NA	NA	NA	NA	NA	NA	NA	0%	NA	0%	-	-	-
	Figure	-	-	-	-	-	-	-	-	-	S214	-	S218	-	-	-

AE: adverse events; CI: confidence interval; NA: not applicable; OR: odds ratio; SAE: serious adverse events
*No studies reported data on the rest of the outcomes

Figures

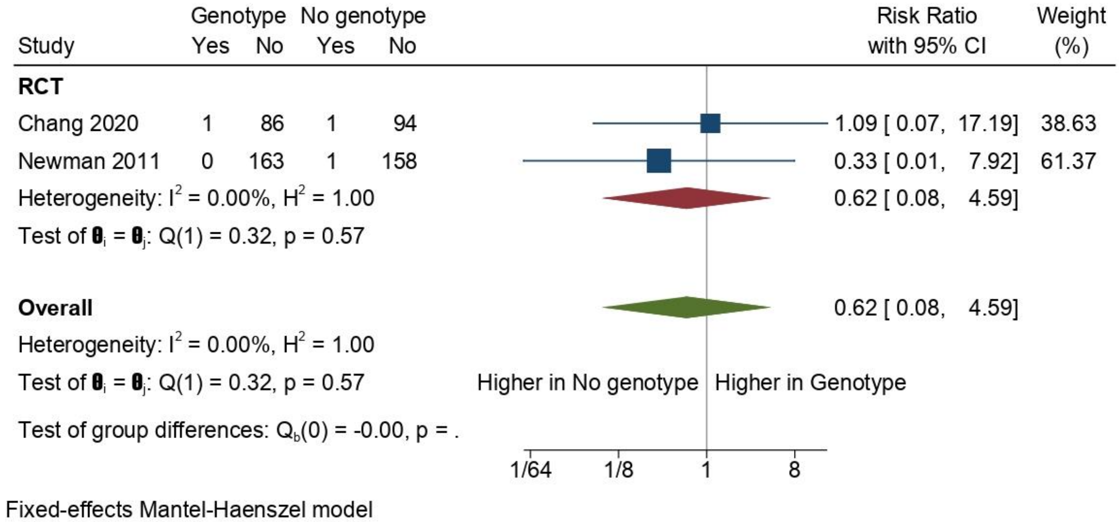


Figure S1. Forest plot of comparison genotyping vs no genotyping, outcome: Total serious adverse events

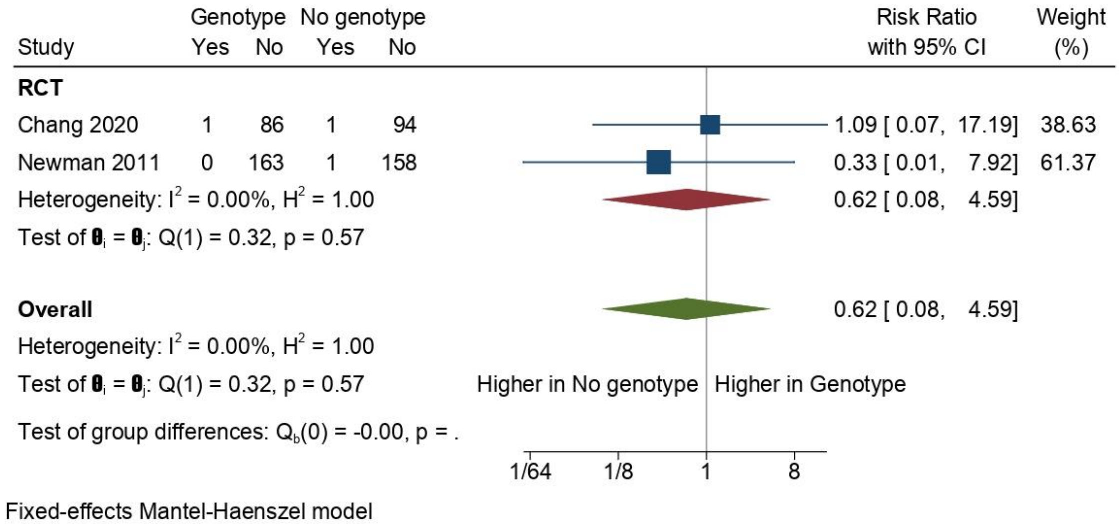

Genotype No genotype
Study Yes No Yes No
Risk Ratio with 95% CI
Weight (%)
RCT
Chang 2020 1 86 1 94 1.09 [0.07, 17.19] 38.63
Newman 2011 0 163 1 158 0.33 [0.01, 7.92] 61.37
Heterogeneity: I² = 0.00%, H² = 1.00 0.62 [0.08, 4.59]
Test of θi = θj: Q(1) = 0.32, p = 0.57
Overall 0.62 [0.08, 4.59]
Heterogeneity: I² = 0.00%, H² = 1.00
Test of θi = θj: Q(1) = 0.32, p = 0.57
Higher in No genotype
Higher in Genotype
Test of group differences: Qb(0) = -0.00, p = .
1/64
1/8
1
8
Fixed-effects Mantel-Haenszel model

Figure S2. Forest plot of comparison genotyping vs no genotyping, outcome: Serious hematologic adverse events

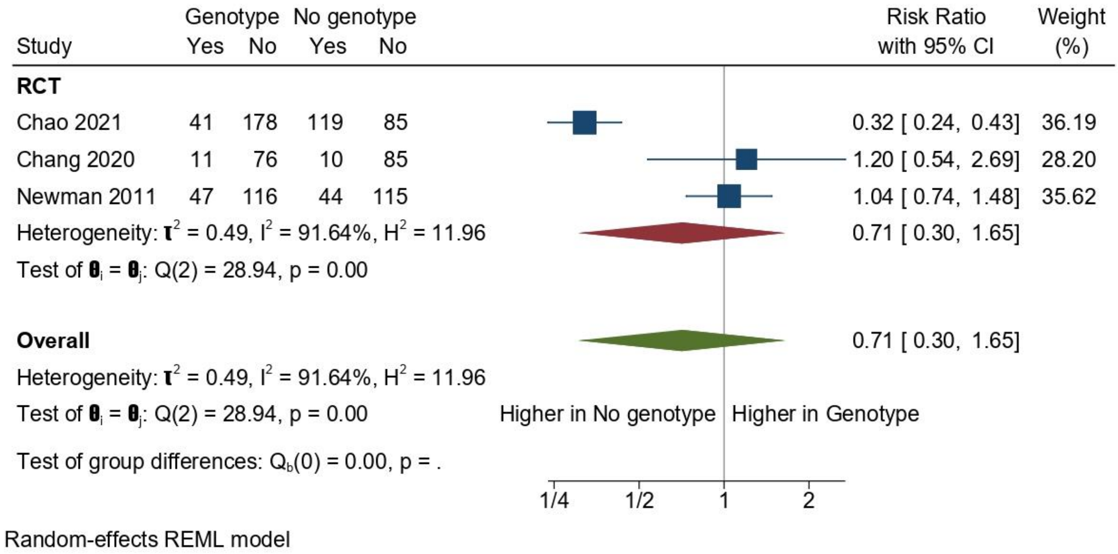


Figure S3. Forest plot of comparison genotyping vs no genotyping, outcome: Withdrawal due to adverse events

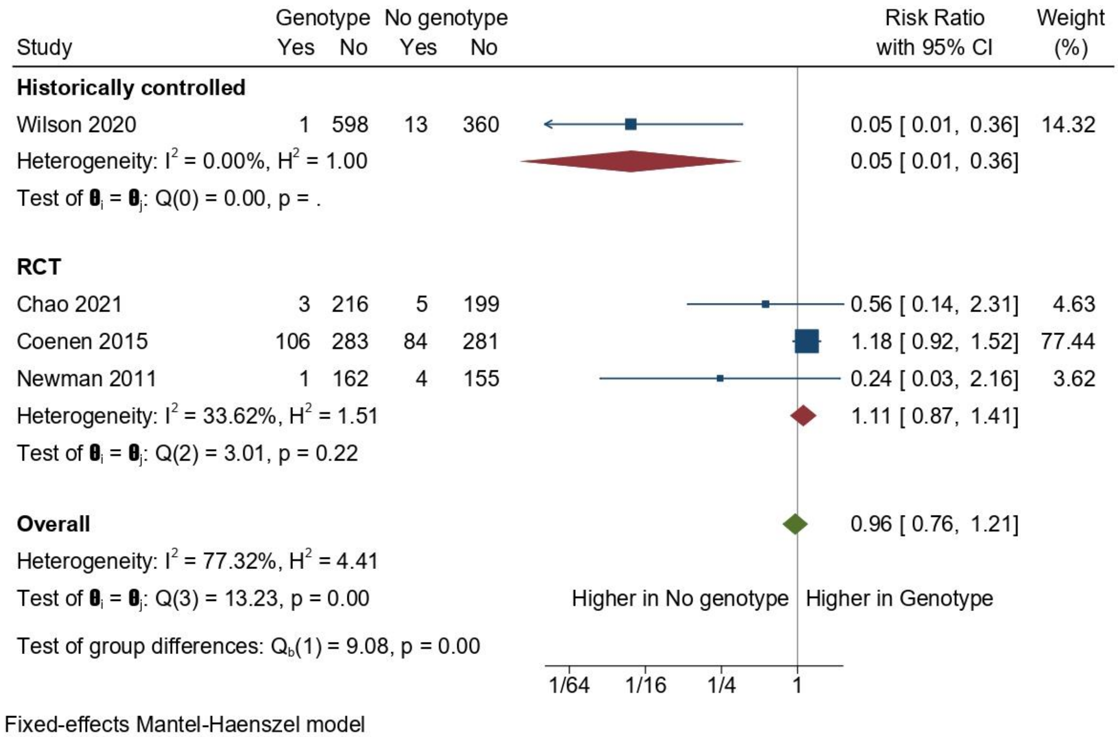


Figure S4. Forest plot of comparison genotyping vs no genotyping, outcome: Pancreatitis

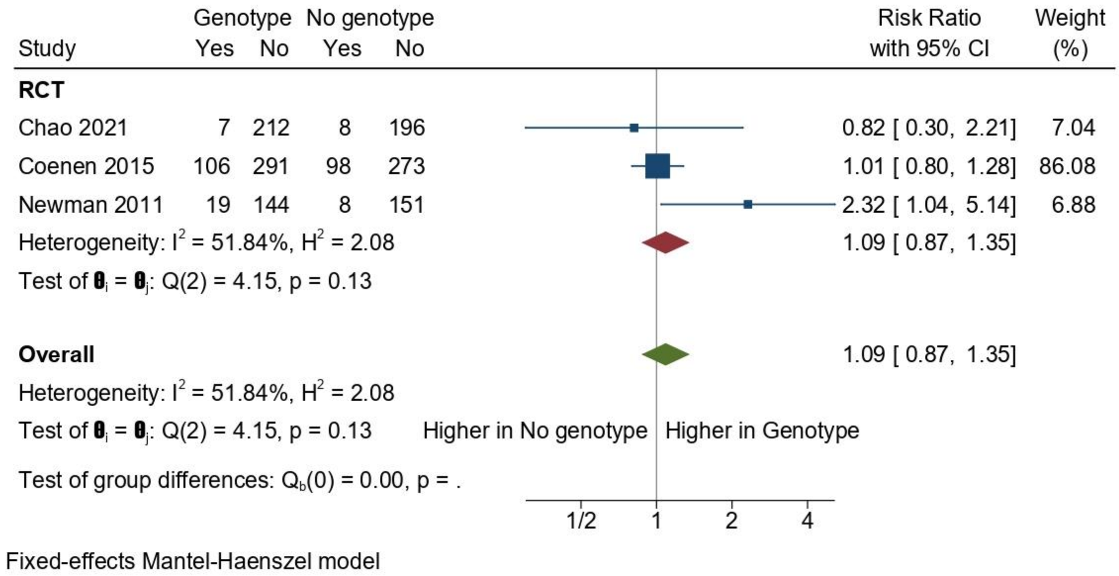


Figure S5. Forest plot of comparison genotyping vs no genotyping, outcome: Hepatotoxicity

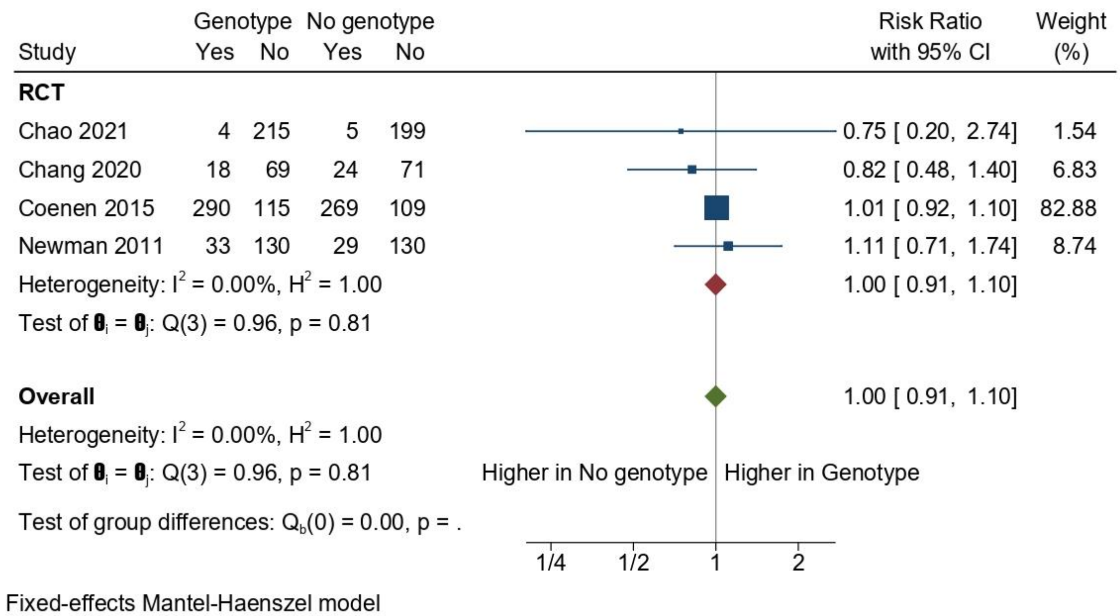


Figure S6. Forest plot of comparison genotyping vs no genotyping, outcome: Gastrointestinal side effects

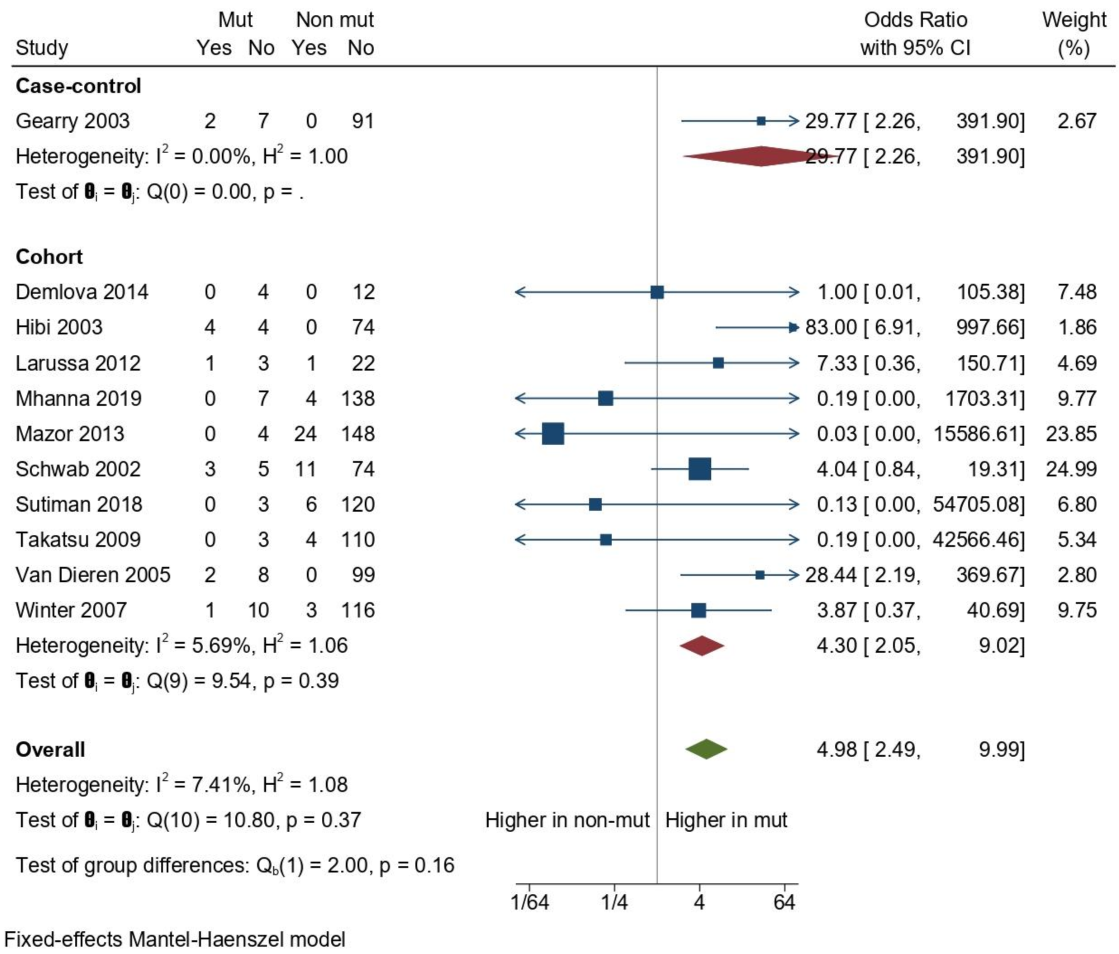


Figure S7. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Total serious adverse events

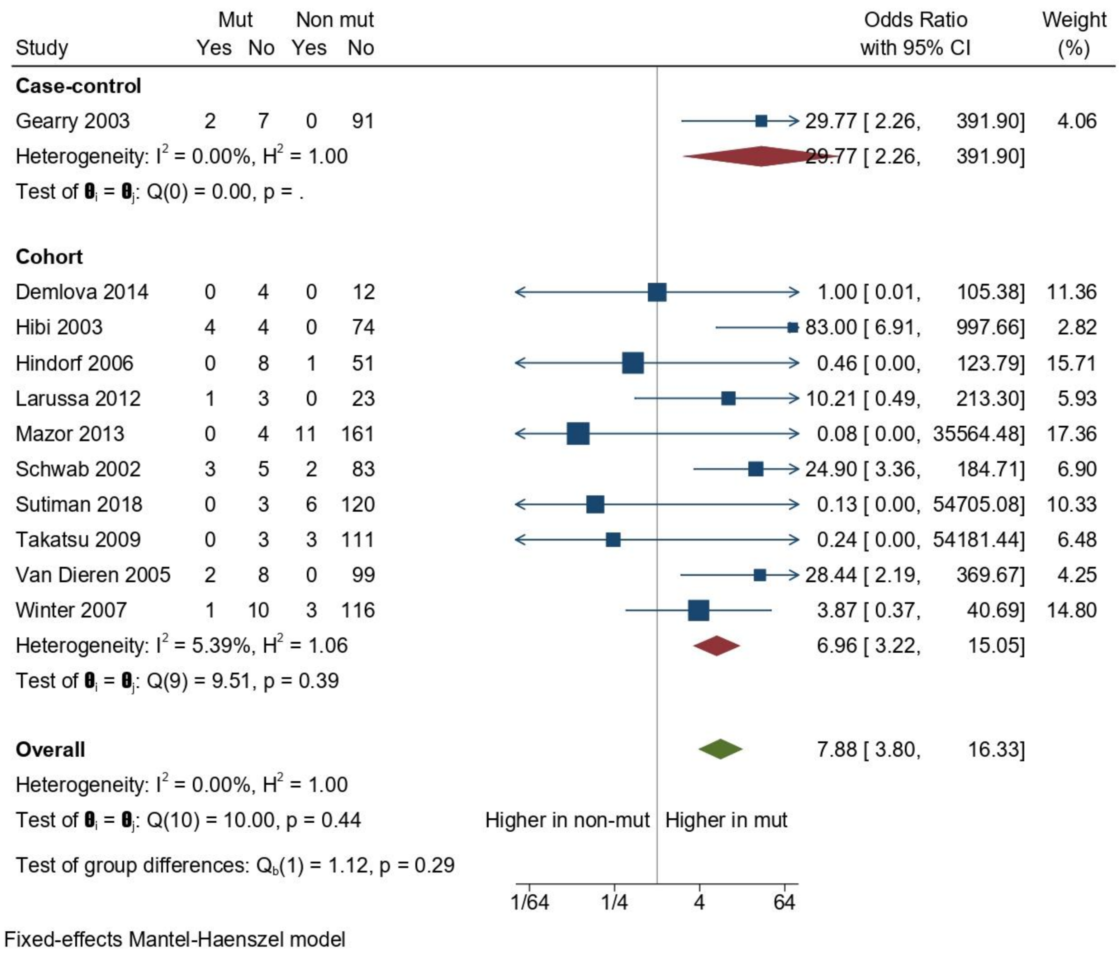


Figure S8. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Serious hematologic adverse events

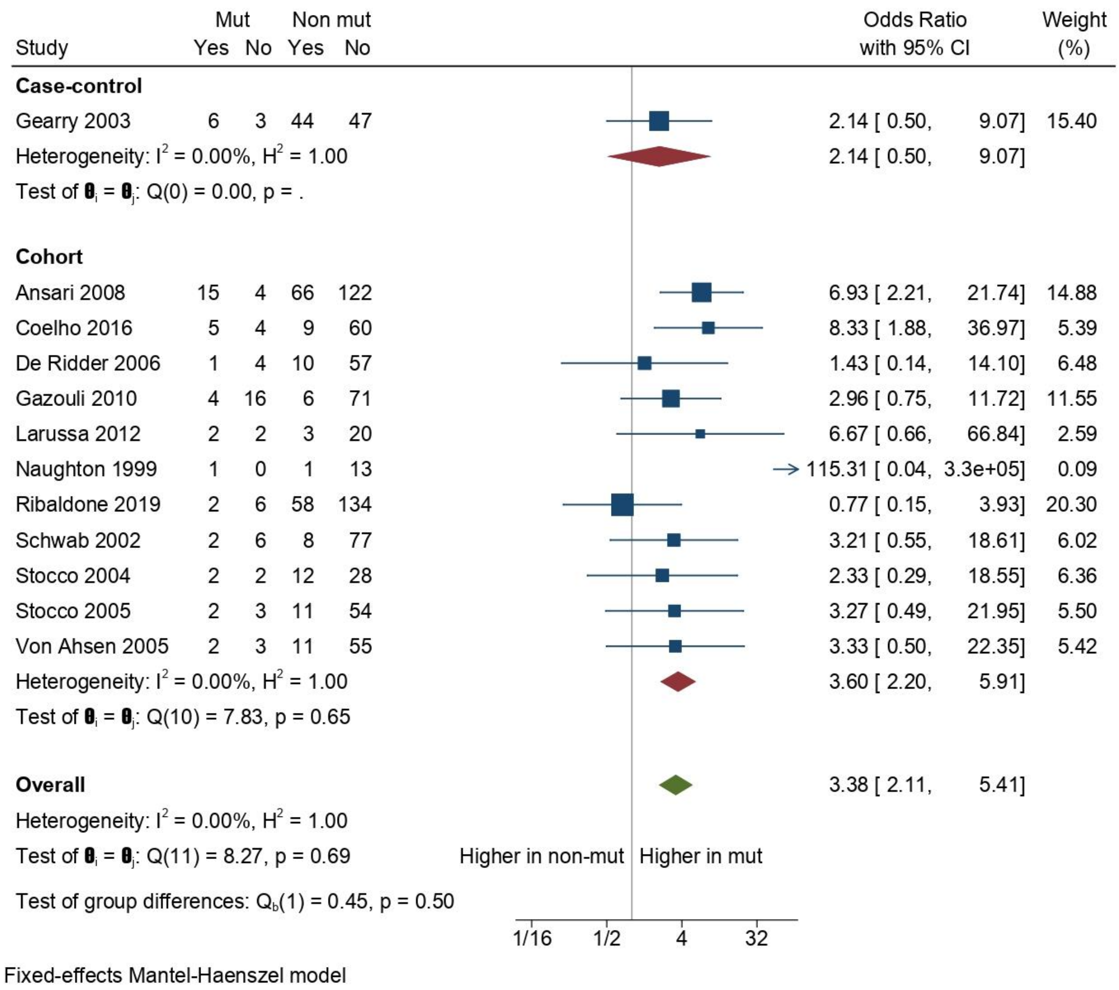


Figure S9. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Withdrawal due to adverse events

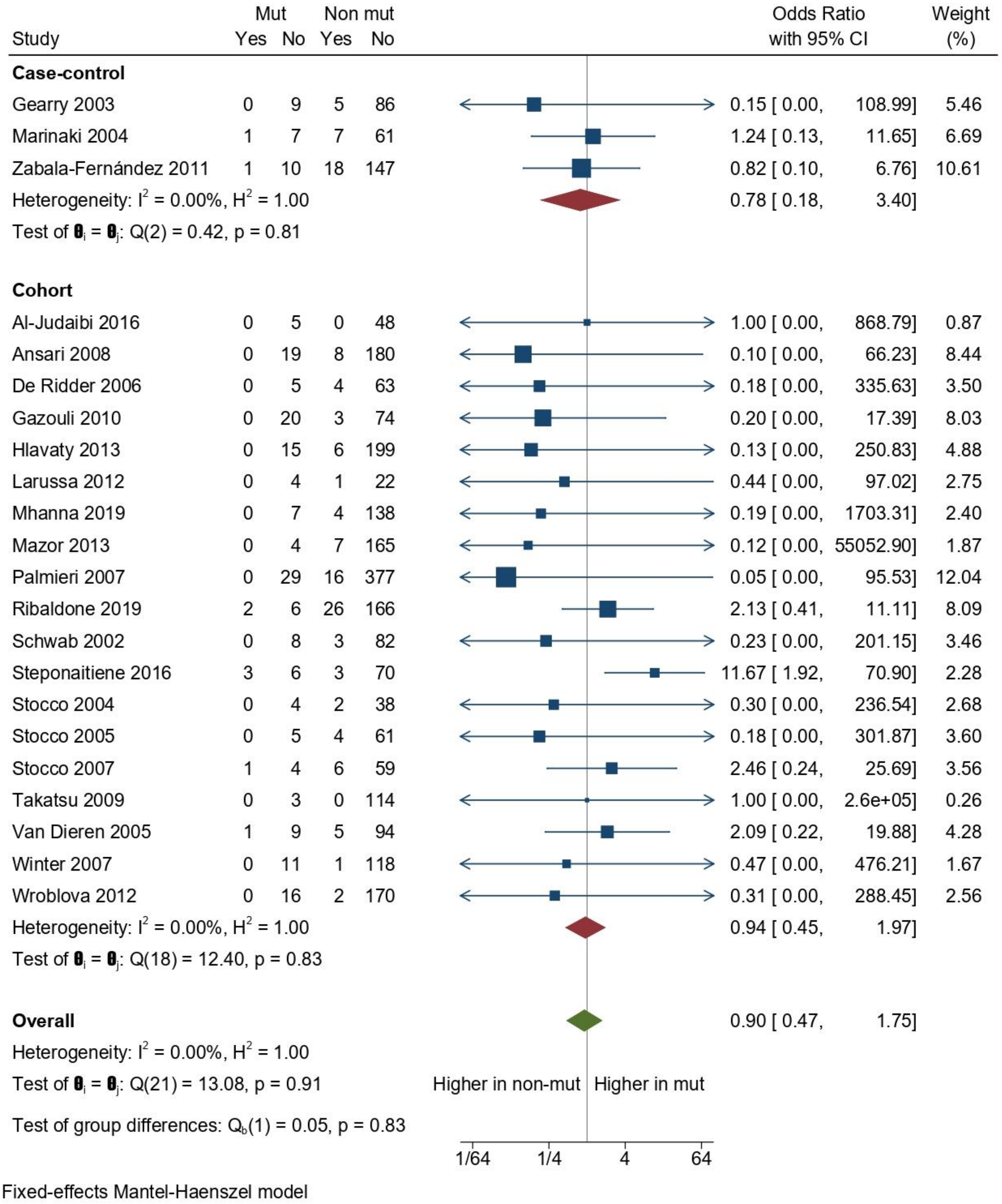


Figure S10. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Pancreatitis

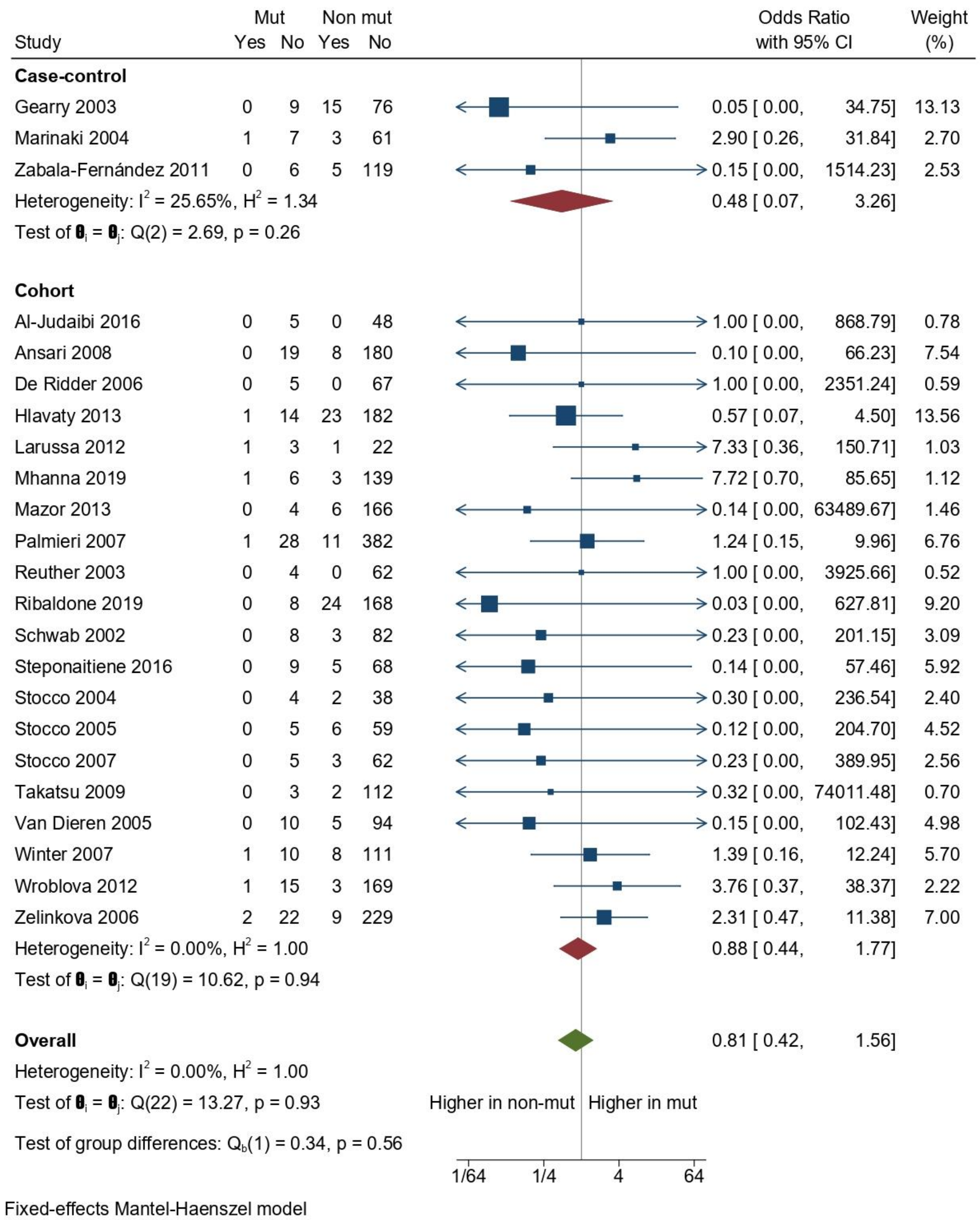


Figure S11. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Hepatotoxicity

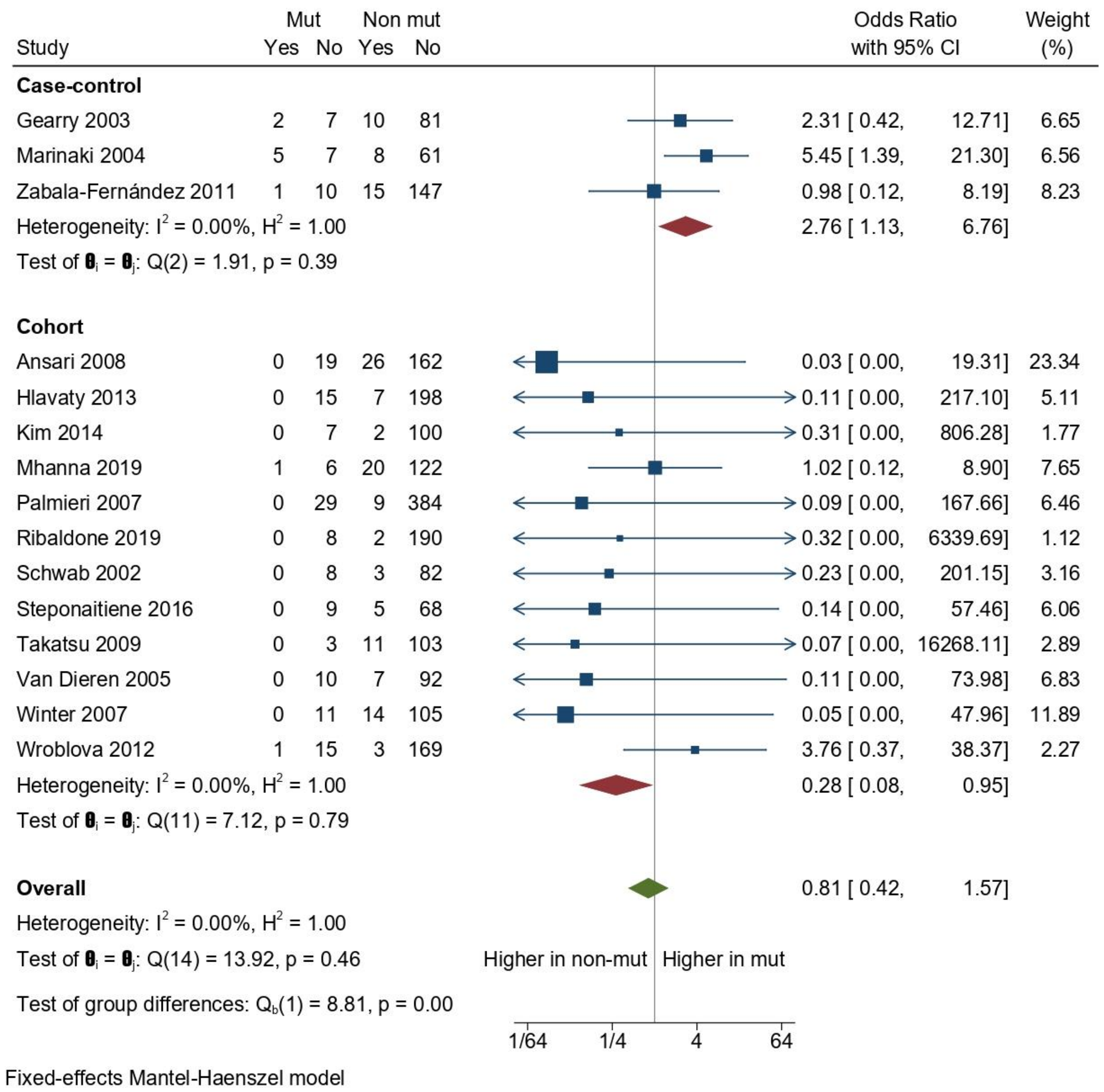


Figure S12. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Gastrointestinal side effects

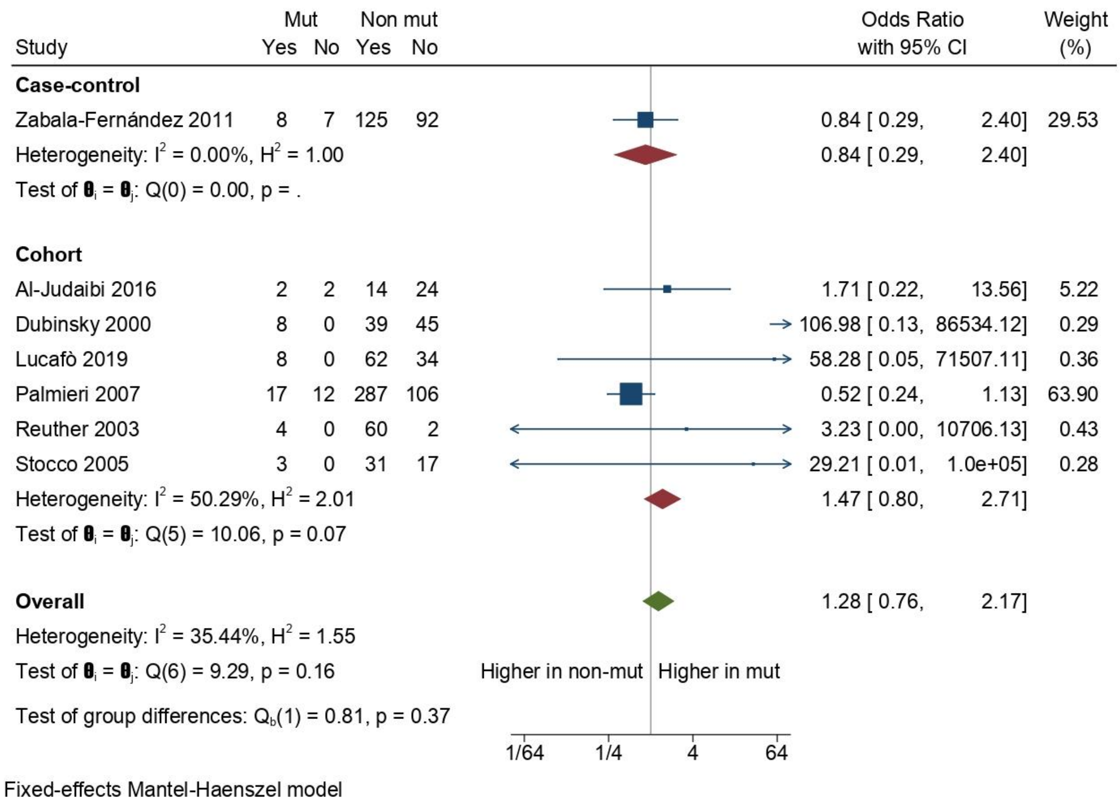
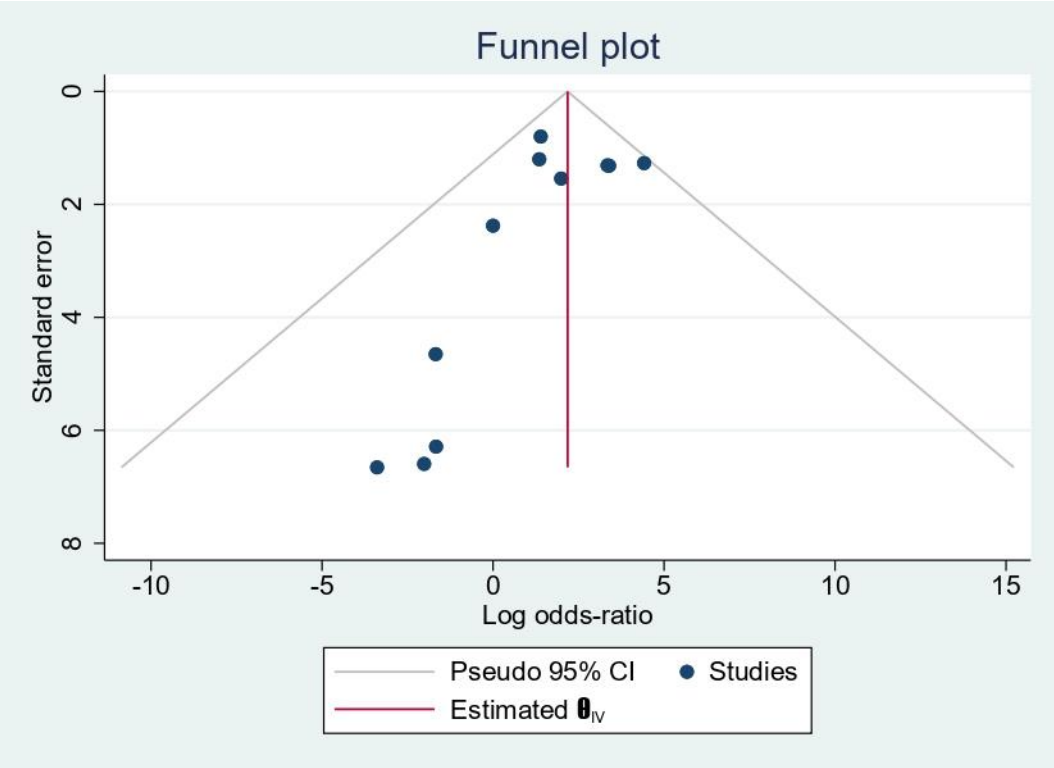
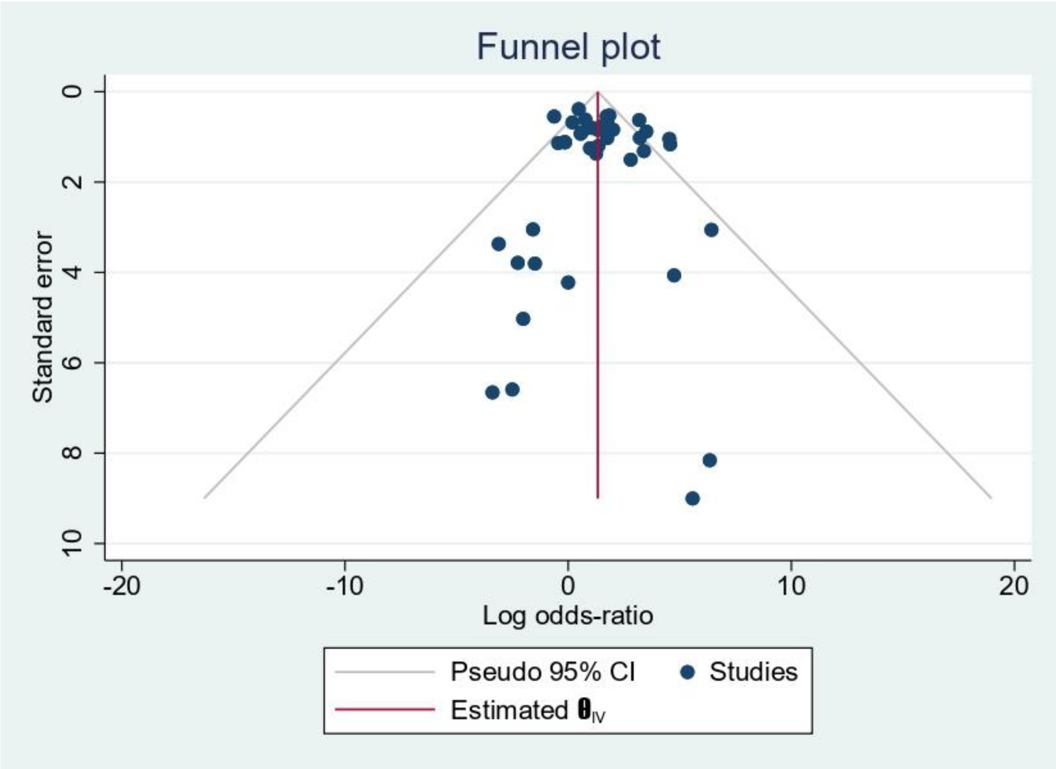


Figure S13. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Clinical remission



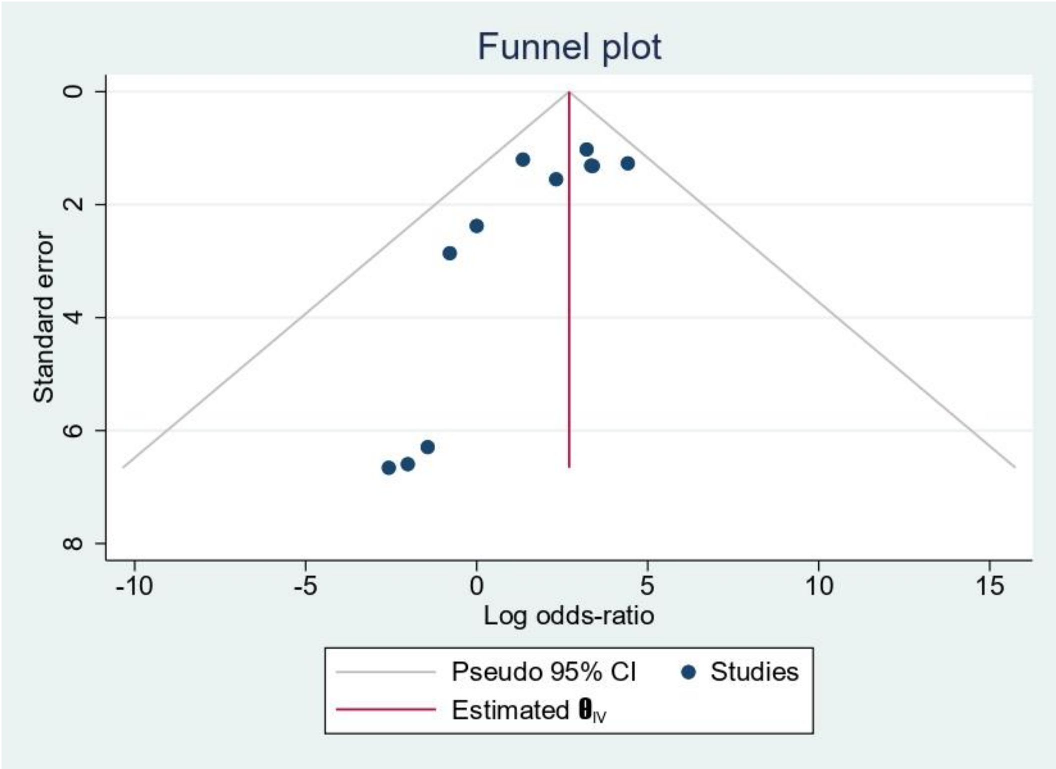
Test for Funnel Plot Asymmetry: z = 10.61, p < 0.001

Figure S14. Funnel plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Total serious adverse events



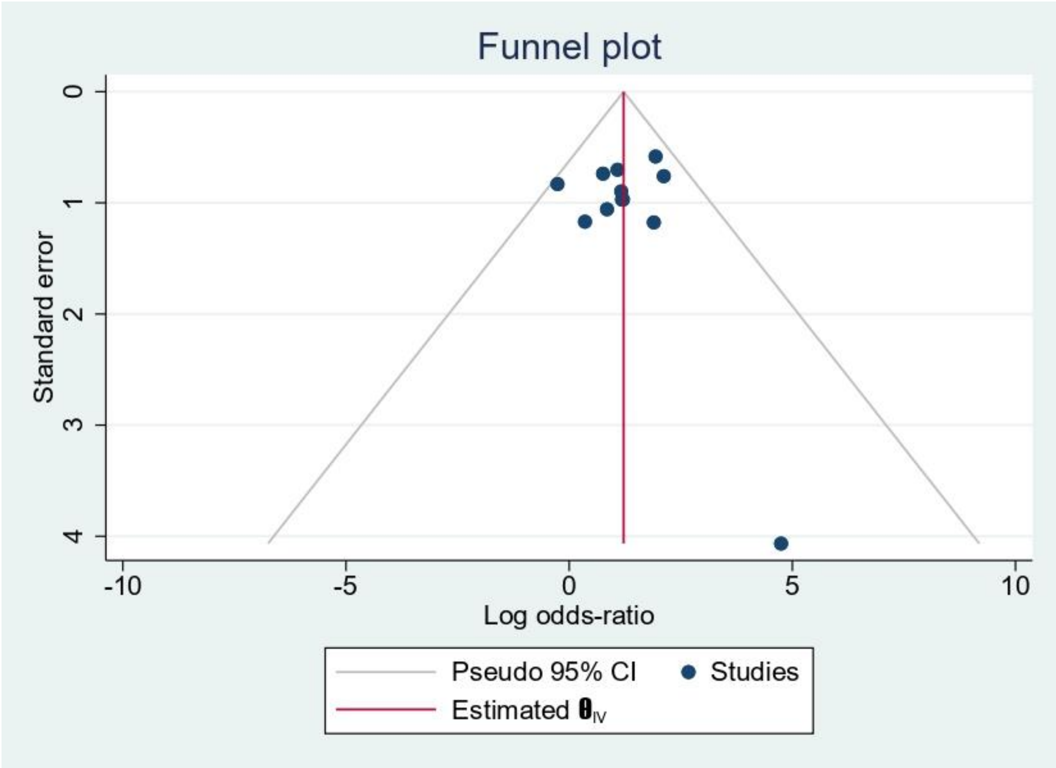
Test for Funnel Plot Asymmetry: z = 11.94, p <0.001

Figure S15. Funnel plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: total hematologic adverse events



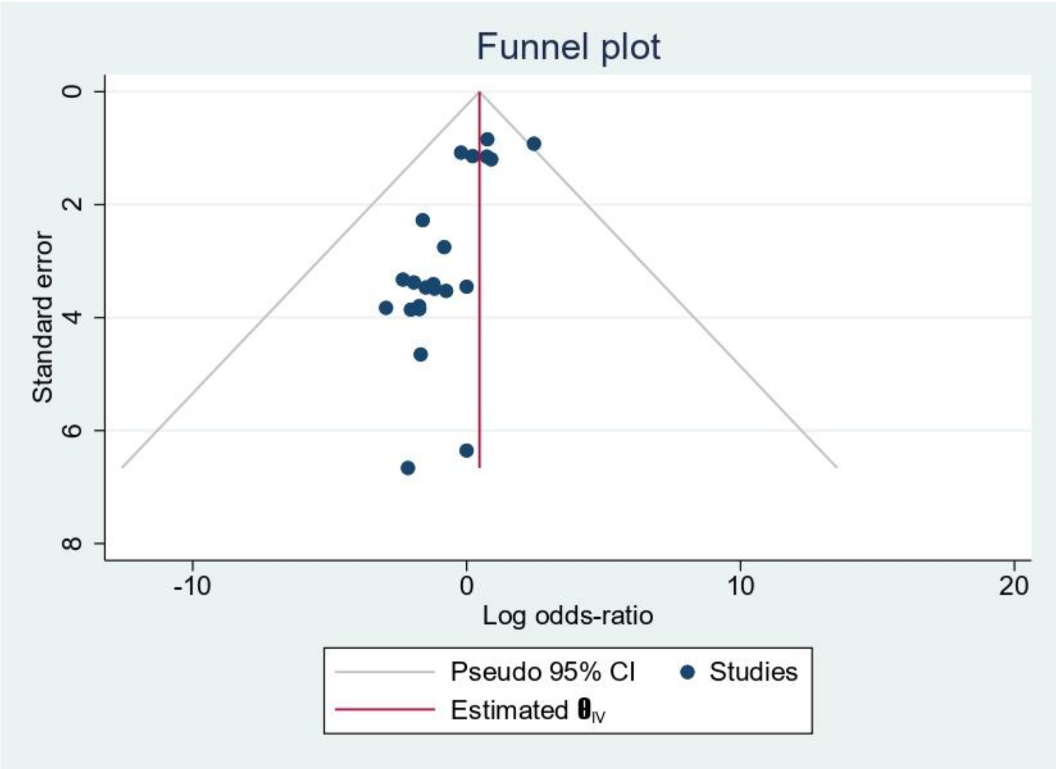
Test for Funnel Plot Asymmetry: z = 7.60, p < 0.001

Figure S16. Funnel plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Serious hematologic adverse events



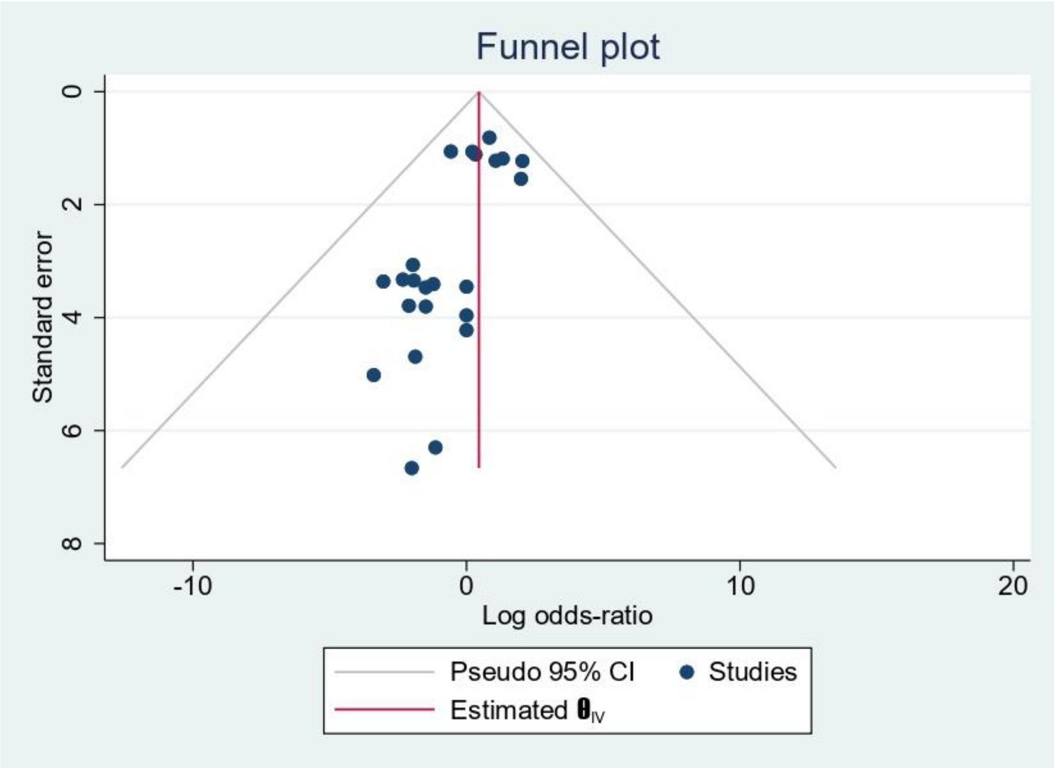
Test for Funnel Plot Asymmetry: $z = 4.42$, $p < 0.001$

Figure S17. Funnel plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Withdrawal due to adverse events



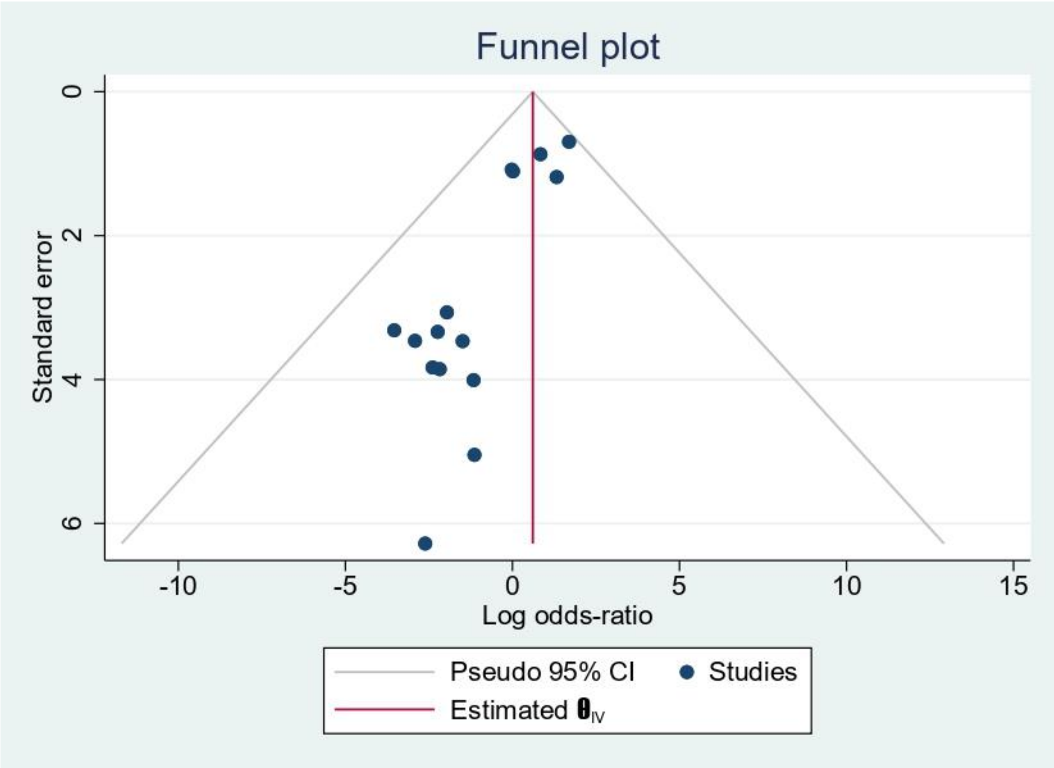
Test for Funnel Plot Asymmetry: z = 4.61, p < 0.001

Figure S18. Funnel plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Pancreatitis



Test for Funnel Plot Asymmetry: z = 0.33, p = 0.7413

Figure S19. Funnel plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Hepatotoxicity



Test for Funnel Plot Asymmetry: z = 9.39, p < 0.001

Figure S20. Funnel plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Gastrointestinal side effects

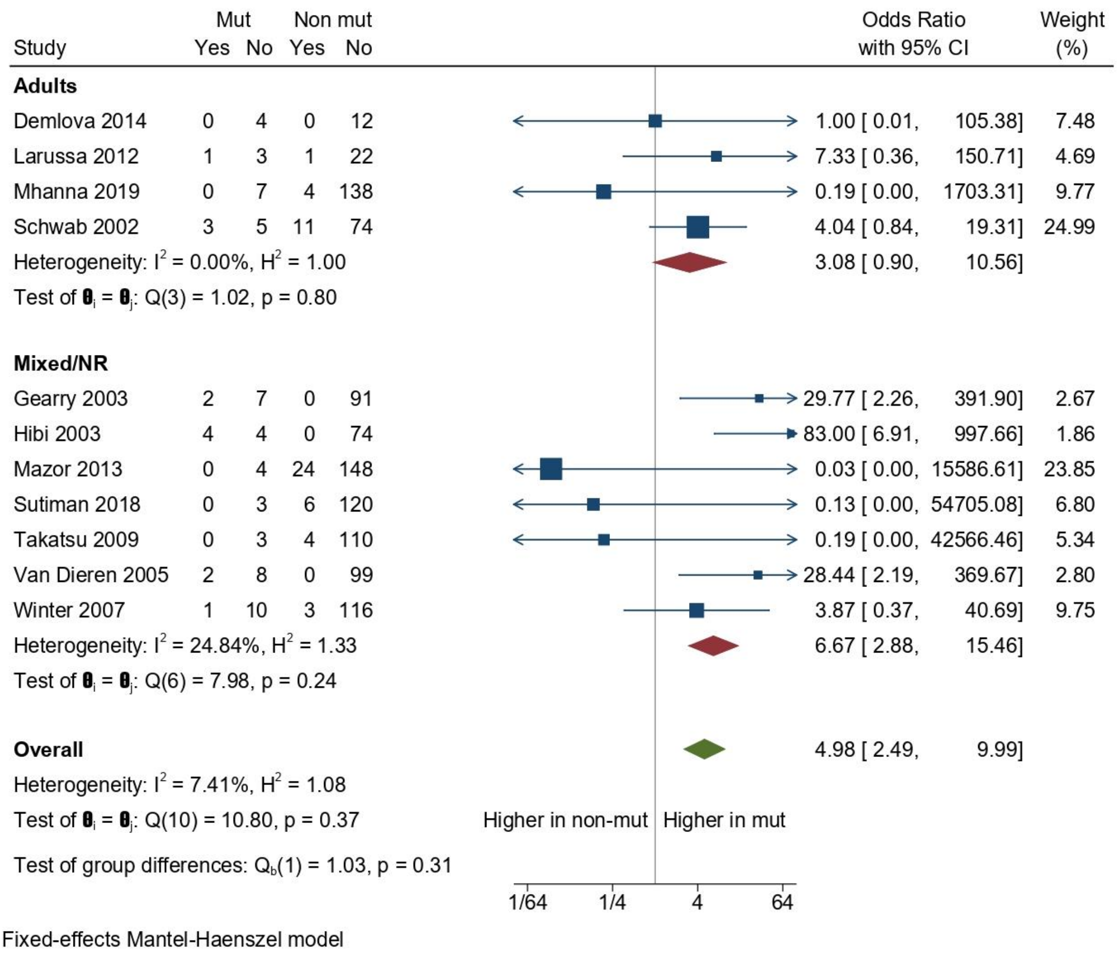
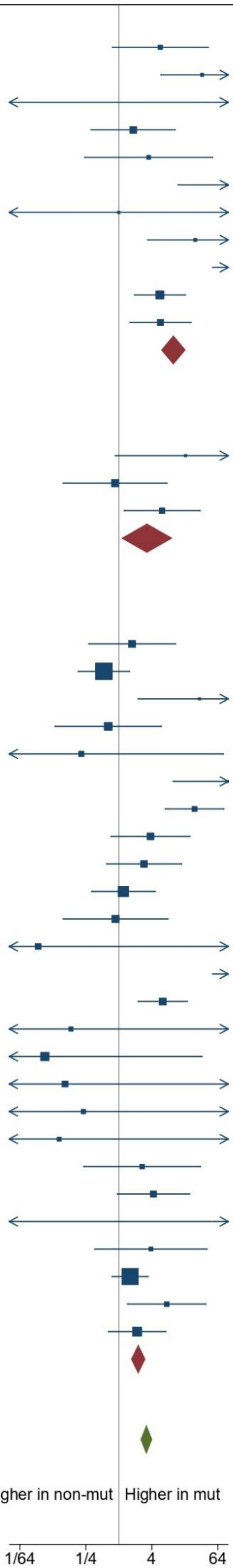


Figure S21. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Total serious adverse events. Subgroup analysis according to age

Study	Mut Yes	Mut No	Non mut Yes	Non mut No	Odds Ratio with 95% CI	Weight (%)
Adults						
Al-Judaibi 2016	2	3	5	43	5.73 [0.76, 42.99]	0.96
Ansari 2008	5	14	2	186	33.21 [5.90, 186.87]	0.46
Fangbin 2016	2	0	24	106	569.50 [0.00, 5.0e+09]	0.01
Hindorf 2006	2	6	8	44	1.83 [0.31, 10.75]	2.71
Larussa 2012	1	3	2	21	3.50 [0.24, 51.46]	0.75
Mhanna 2019	4	3	2	140	93.33 [12.05, 722.62]	0.14
Reuther 2003	0	4	0	62	1.00 [0.00, 3925.66]	0.19
Schwab 2002	3	5	2	83	24.90 [3.36, 184.71]	0.36
Steponaitiene 2016	9	0	8	65	615.16 [1.54, 2.5e+05]	0.04
Wroblova 2012	8	8	26	146	5.62 [1.94, 16.29]	3.75
Zelinkova 2006	4	20	8	230	5.75 [1.59, 20.77]	2.07
Heterogeneity: I^2 = 36.71%, H^2 = 1.58					9.87 [5.92, 16.46]	
Test of $\theta_i = \theta_j$: Q(10) = 15.80, p = 0.11						
Children						
De Ridder 2006	1	4	1	66	16.50 [0.86, 315.19]	0.19
Dubinsky 2000	1	7	12	72	0.86 [0.10, 7.60]	3.09
Gazouli 2010	4	16	3	74	6.17 [1.26, 30.29]	1.68
Heterogeneity: I^2 = 37.92%, H^2 = 1.61					3.25 [1.11, 9.47]	
Test of $\theta_i = \theta_j$: Q(2) = 3.22, p = 0.20						
Mixed/NR						
Asada 2016	2	3	43	113	1.75 [0.28, 10.85]	2.71
Chao 2017	4	23	173	532	0.53 [0.18, 1.57]	18.40
Gearry 2003	2	7	0	91	29.77 [2.26, 391.90]	0.21
Grover 2020	1	4	32	82	0.64 [0.07, 5.95]	3.64
Hawwa 2008	0	4	3	28	0.21 [0.00, 81.03]	1.46
Hibi 2003	7	1	5	69	96.60 [9.85, 947.70]	0.21
Hlavaty 2013	11	4	21	184	24.10 [7.04, 82.45]	1.29
Kim 2010	5	2	111	168	3.78 [0.72, 19.85]	2.63
Kim 2014	3	4	21	81	2.89 [0.60, 13.93]	2.61
Kim 2017	4	5	128	194	1.21 [0.32, 4.60]	6.55
Marinaki 2004	1	7	10	61	0.87 [0.10, 7.86]	3.00
Mazor 2013	0	4	24	148	0.03 [0.00, 15586.61]	1.91
Naughton 1999	1	0	1	13	115.31 [0.04, 3.3e+05]	0.03
Palmieri 2007	6	21	17	376	6.32 [2.26, 17.69]	2.88
Ribaldone 2019	0	8	6	186	0.13 [0.00, 2541.91]	0.94
Stocco 2004	0	4	13	27	0.04 [0.00, 32.90]	4.19
Stocco 2005	0	5	7	58	0.10 [0.00, 175.09]	1.89
Stocco 2007	0	5	3	62	0.23 [0.00, 389.95]	0.94
Sutiman 2018	0	3	10	116	0.08 [0.00, 33361.89]	0.86
Takatsu 2009	1	2	18	96	2.67 [0.23, 30.99]	1.04
Van Dieren 2005	3	7	9	90	4.29 [0.94, 19.52]	1.96
Wang 2018	1	0	18	61	264.44 [0.00, 1.2e+10]	0.01
Winter 2007	1	10	3	116	3.87 [0.37, 40.69]	0.78
Yang 2014	13	15	333	617	1.61 [0.76, 3.42]	17.29
Zabala-Fernández 2011	3	4	9	90	7.50 [1.45, 38.91]	1.15
Zhu 2019	4	9	68	330	2.16 [0.65, 7.21]	5.04
Heterogeneity: I^2 = 51.40%, H^2 = 2.06					2.26 [1.67, 3.04]	
Test of $\theta_i = \theta_j$: Q(25) = 51.44, p = 0.00						
Overall					3.18 [2.49, 4.06]	
Heterogeneity: I^2 = 52.18%, H^2 = 2.09						
Test of $\theta_i = \theta_j$: Q(39) = 81.56, p = 0.00						
Test of group differences: $Q_b(2)$ = 23.85, p = 0.00						



Fixed-effects Mantel-Haenszel model

Figure S22. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Total hematologic adverse events. Subgroup analysis according to age

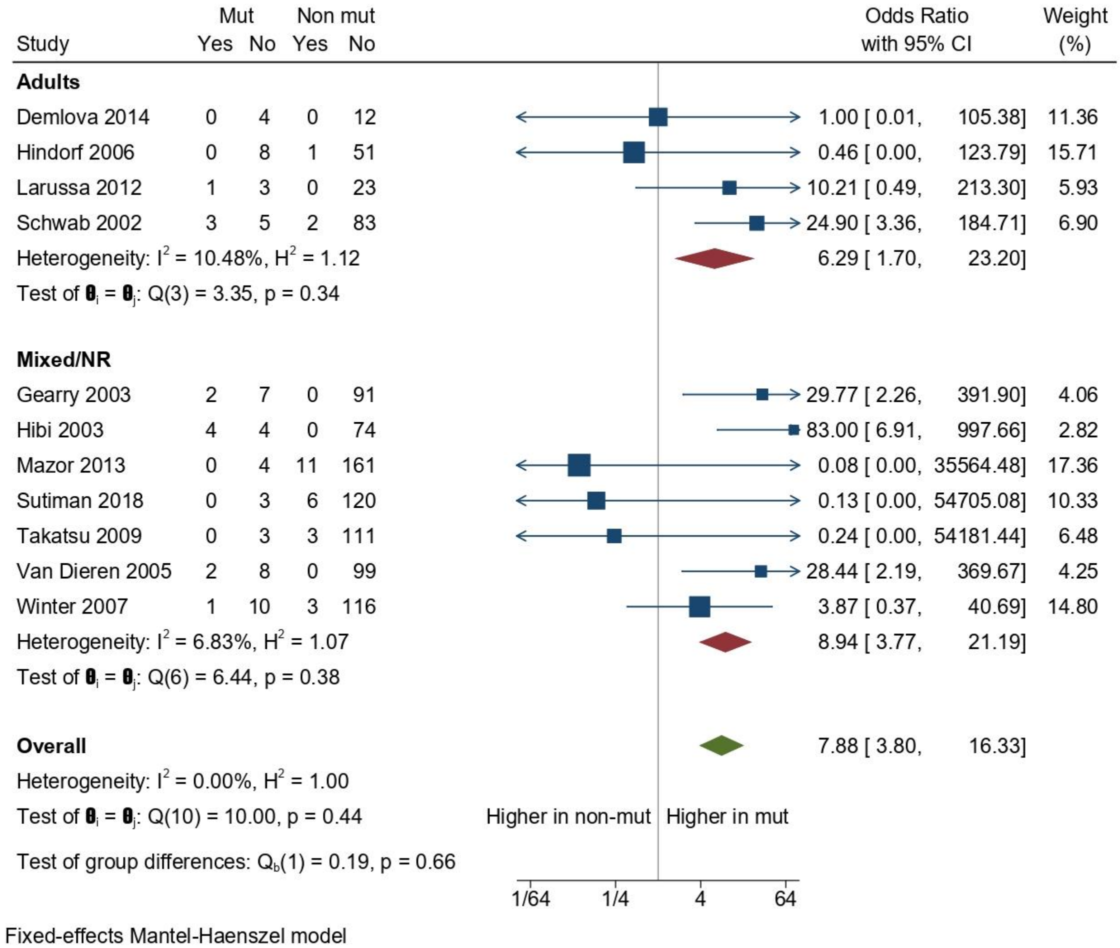


Figure S23. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Serious hematologic adverse events. Subgroup analysis according to age

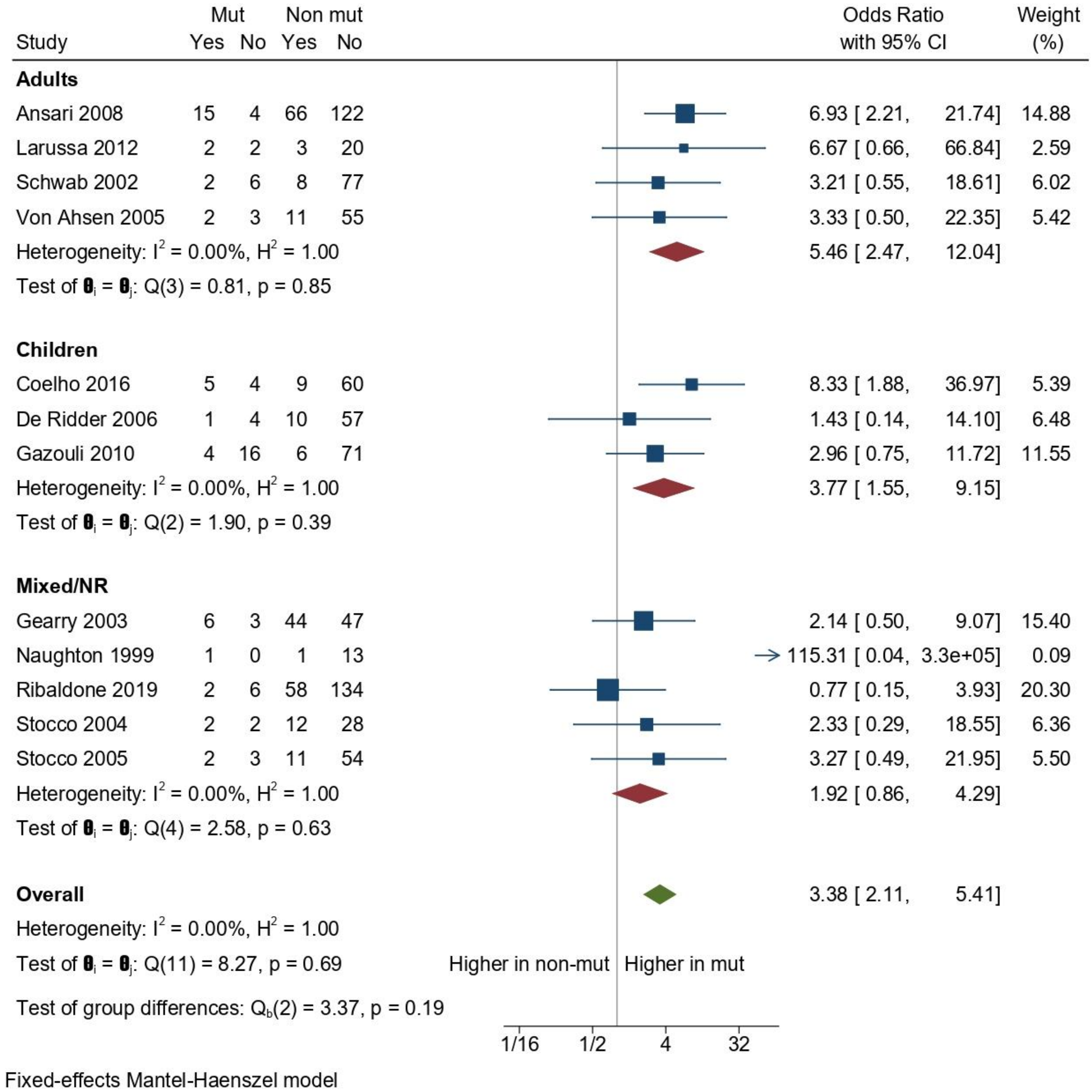


Figure S24. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Withdrawal due to adverse events. Subgroup analysis according to age

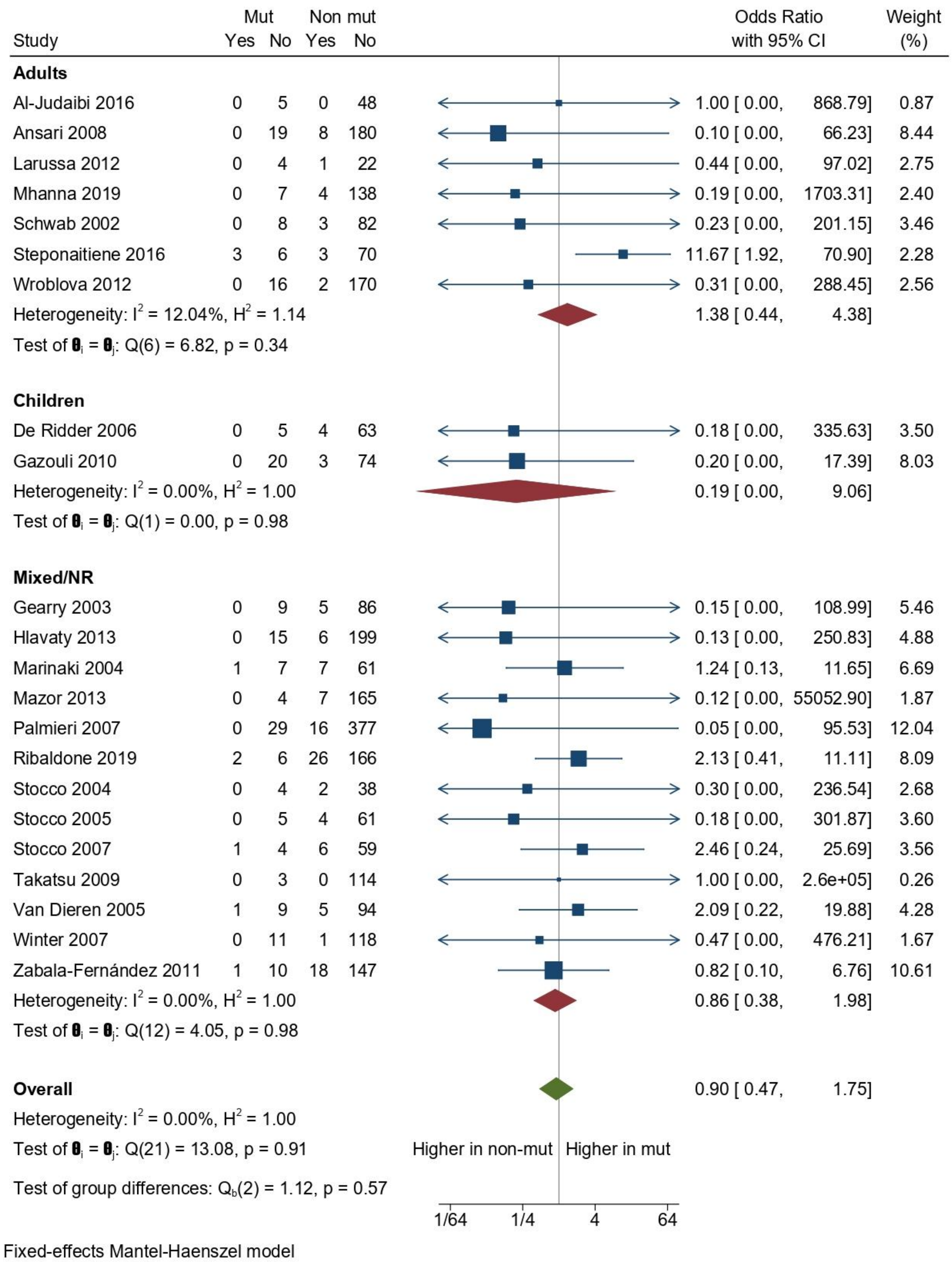


Figure S25. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Pancreatitis. Subgroup analysis according to age

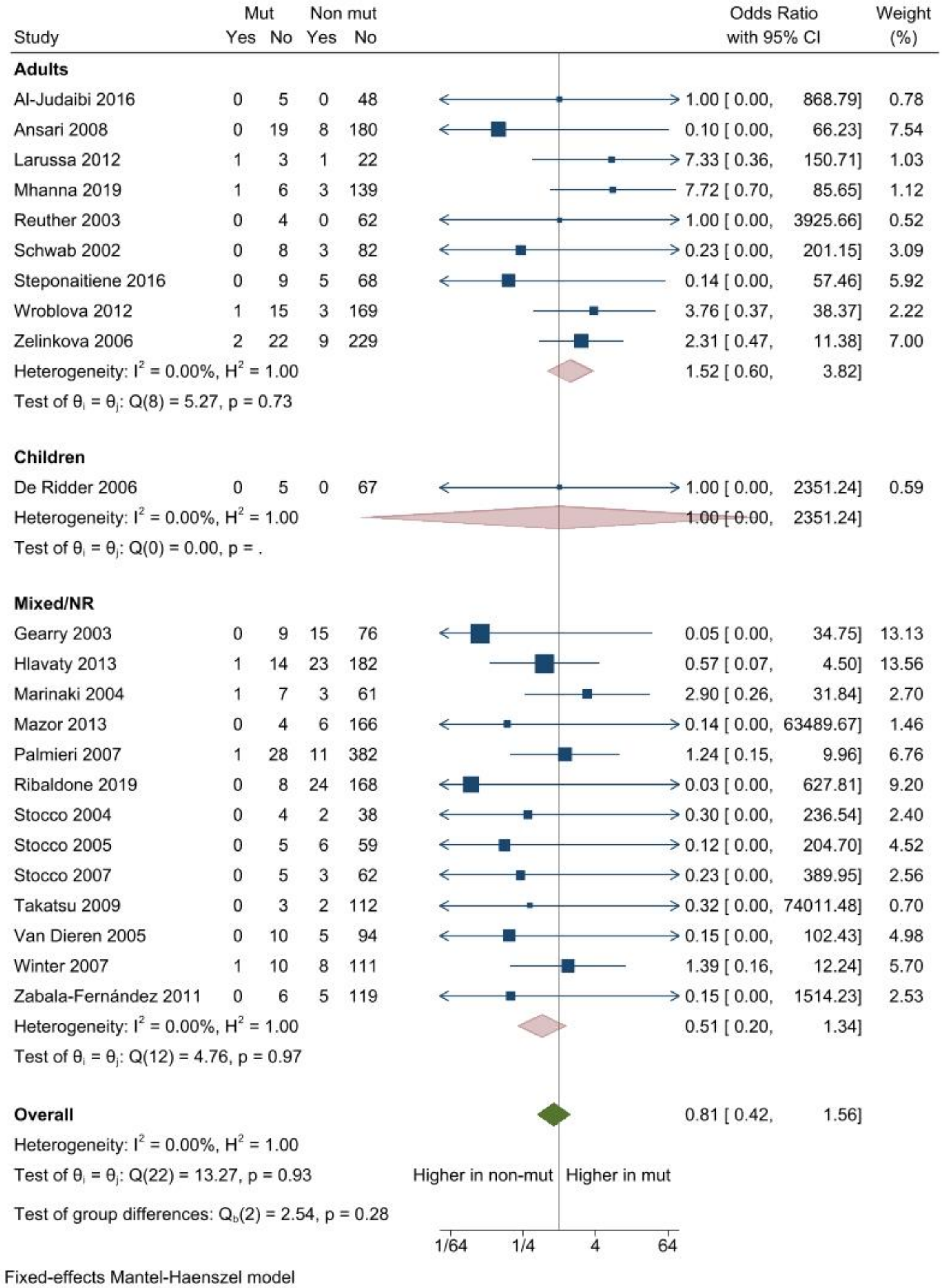


Figure S26. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Hepatotoxicity. Subgroup analysis according to age

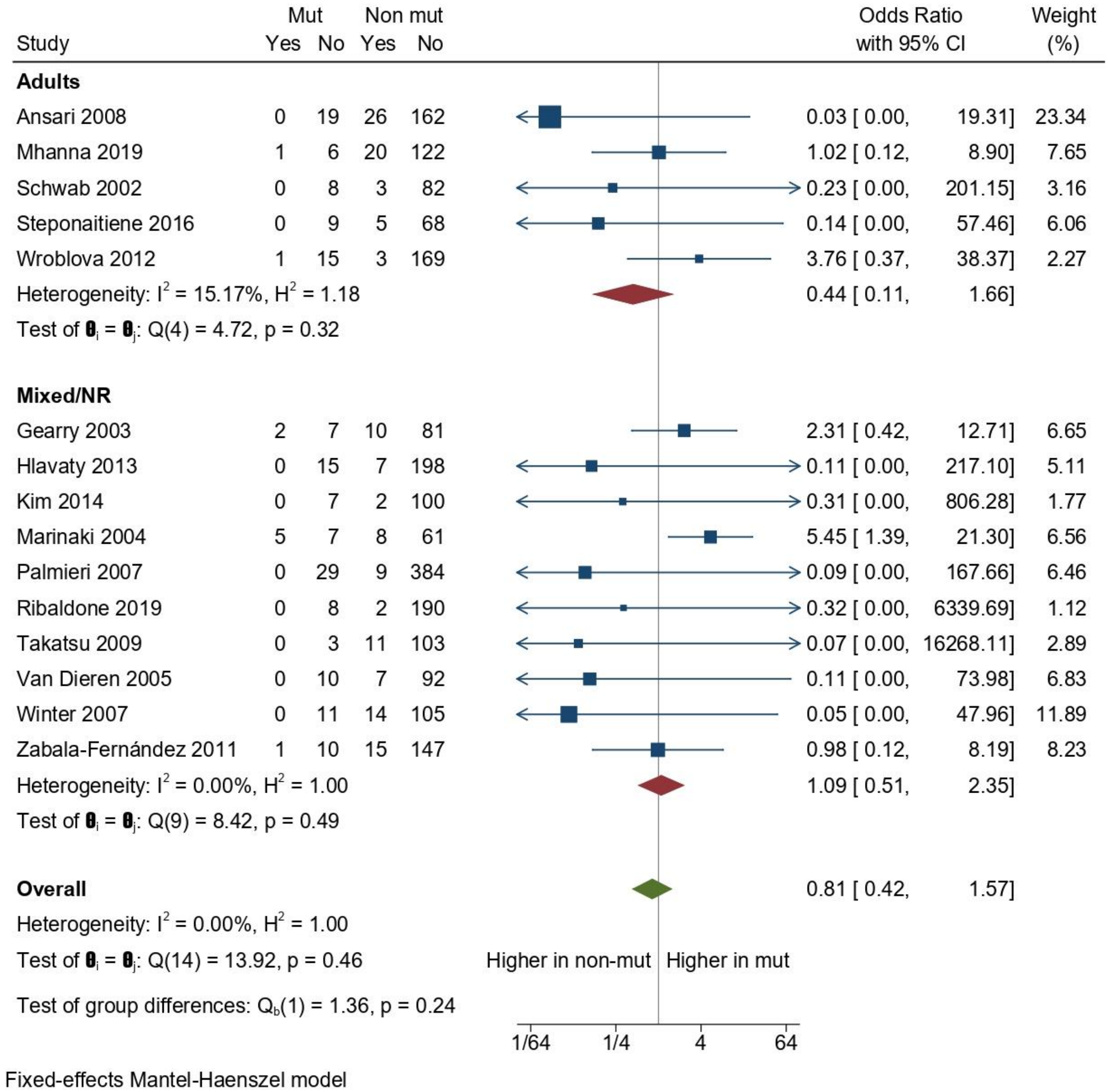


Figure S27. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Gastrointestinal side effects. Subgroup analysis according to age

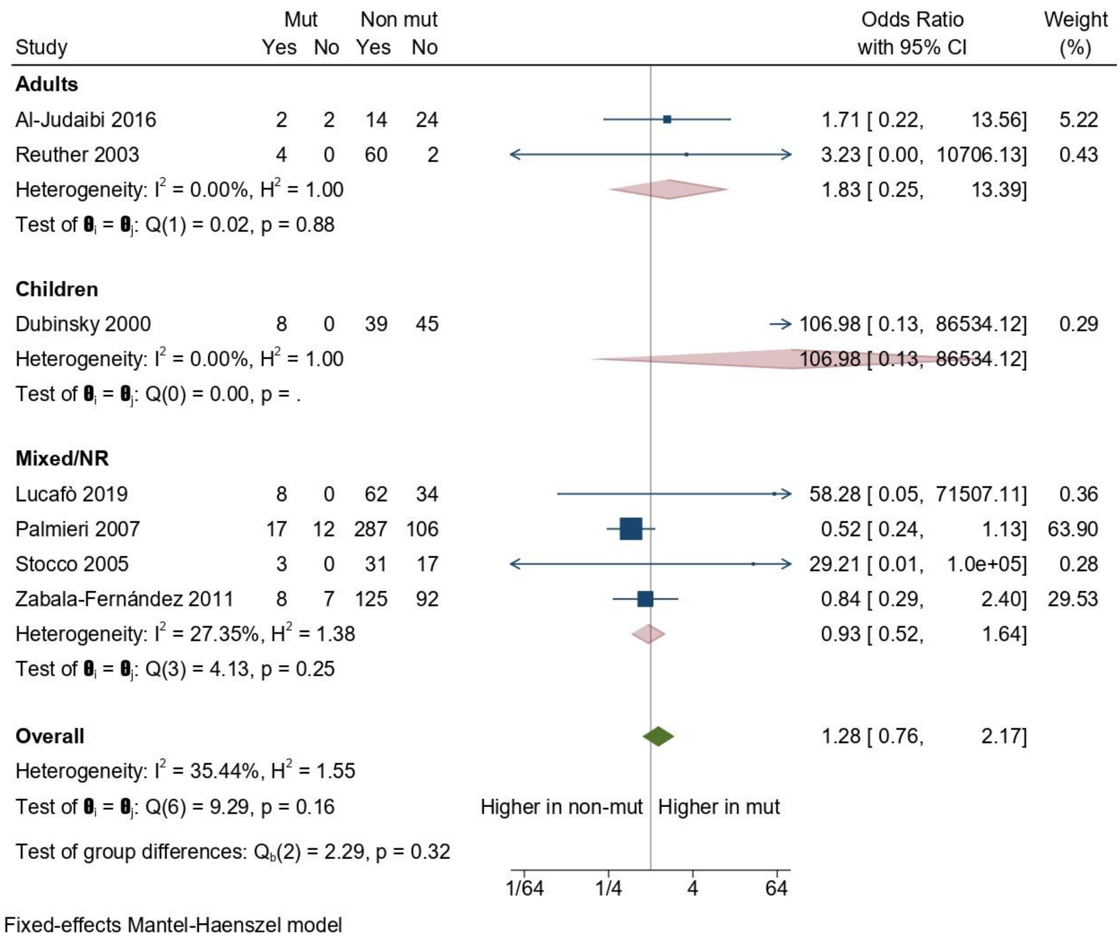


Figure S28. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Clinical remission. Subgroup analysis according to age

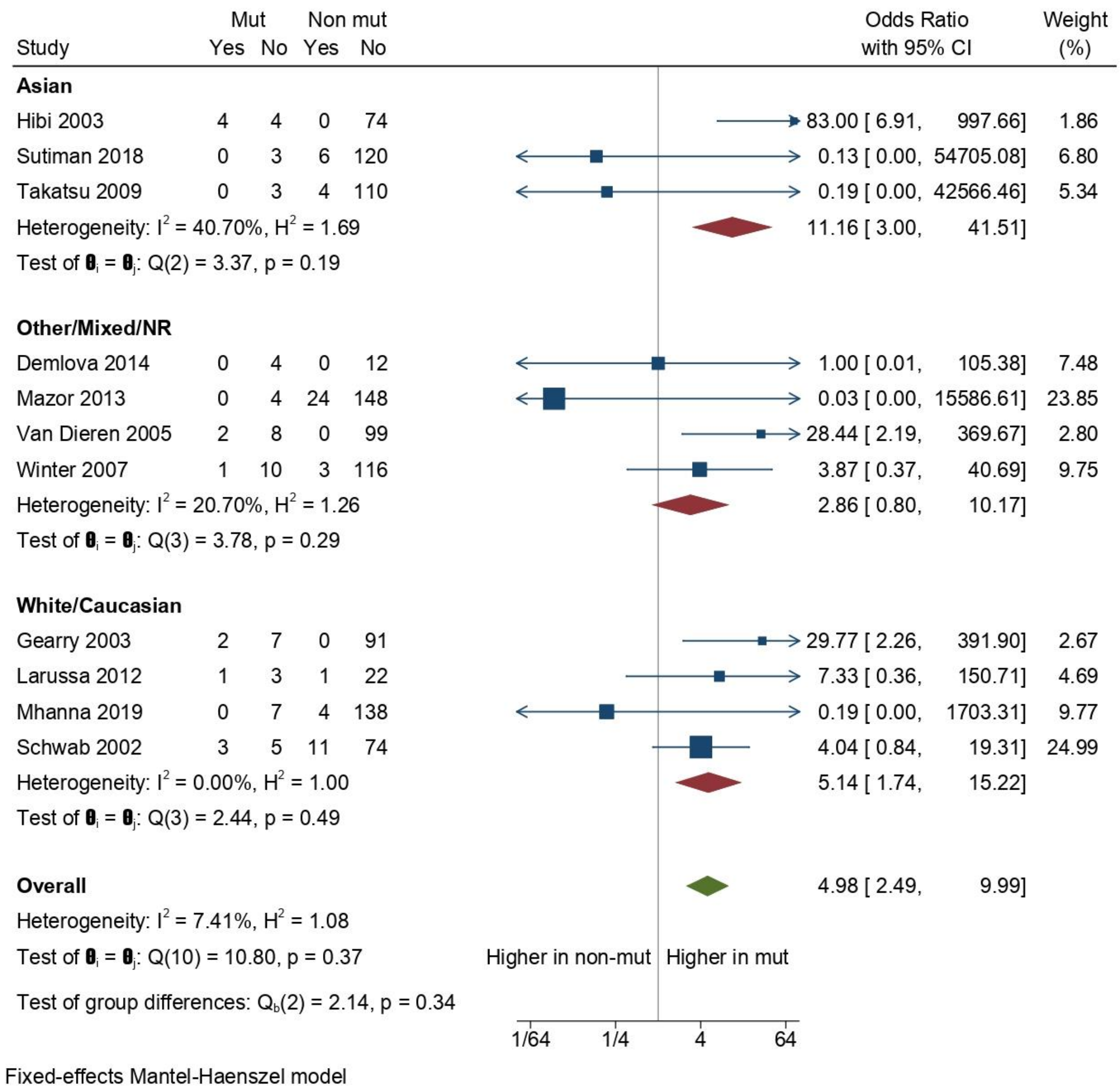


Figure S29. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Total serious adverse events. Subgroup analysis according to race

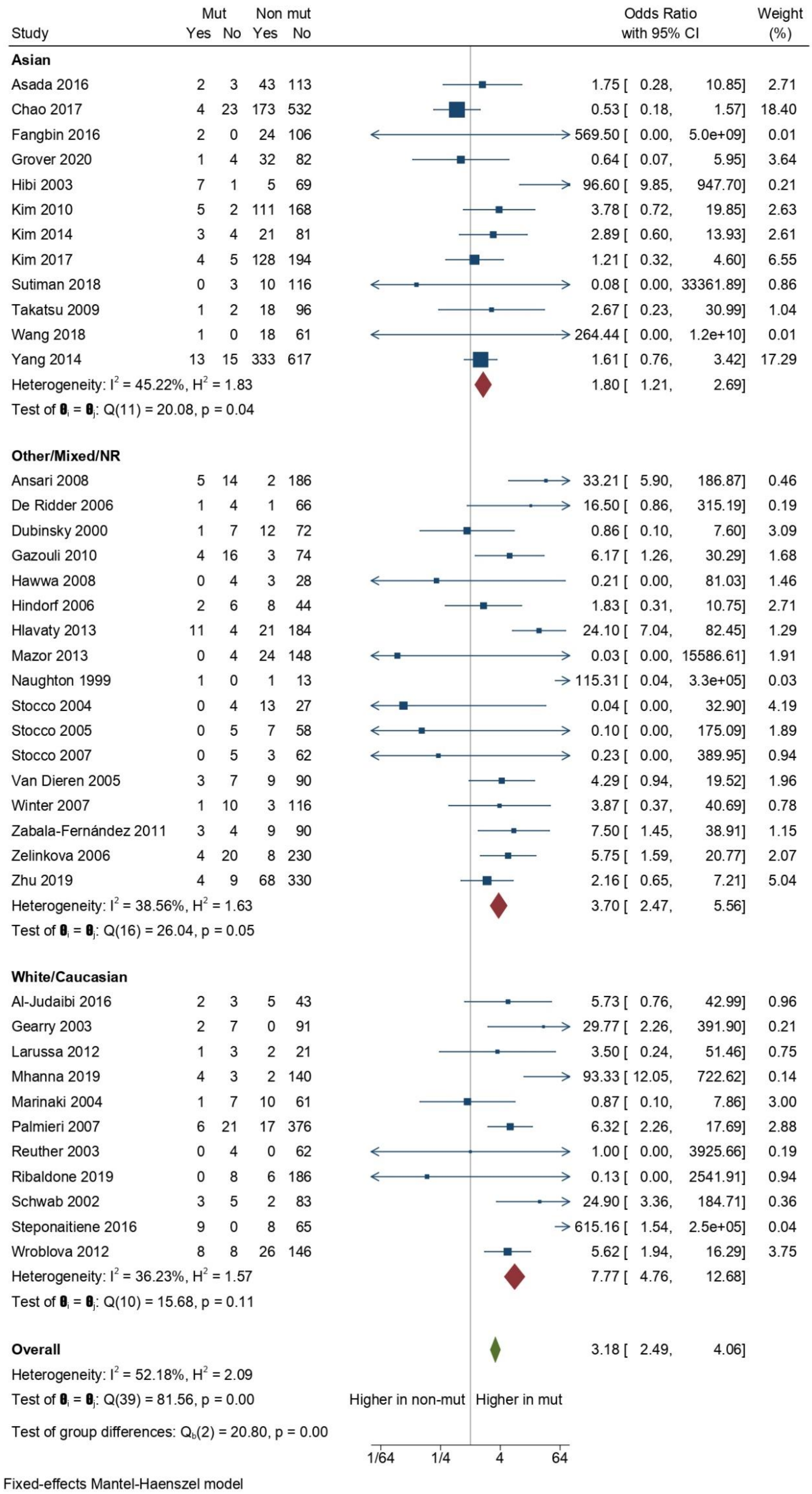

Study | Mut Yes | Mut No | Non mut Yes | Non mut No | Odds Ratio with 95% CI | Weight (%)
Asian
Asada 2016 2 3 43 113 1.75 [0.28, 10.85] 2.71
Chao 2017 4 23 173 532 0.53 [0.18, 1.57] 18.40
Fangbin 2016 2 0 24 106 569.50 [0.00, 5.0e+09] 0.01
Grover 2020 1 4 32 82 0.64 [0.07, 5.95] 3.64
Hibi 2003 7 1 5 69 96.60 [9.85, 947.70] 0.21
Kim 2010 5 2 111 168 3.78 [0.72, 19.85] 2.63
Kim 2014 3 4 21 81 2.89 [0.60, 13.93] 2.61
Kim 2017 4 5 128 194 1.21 [0.32, 4.60] 6.55
Sutiman 2018 0 3 10 116 0.08 [0.00, 33361.89] 0.86
Takatsu 2009 1 2 18 96 2.67 [0.23, 30.99] 1.04
Wang 2018 1 0 18 61 264.44 [0.00, 1.2e+10] 0.01
Yang 2014 13 15 333 617 1.61 [0.76, 3.42] 17.29
Heterogeneity: I^2 = 45.22%, H^2 = 1.83 1.80 [1.21, 2.69]
Test of $\theta_i = \theta_j$: Q(11) = 20.08, p = 0.04
Other/Mixed/NR
Ansari 2008 5 14 2 186 33.21 [5.90, 186.87] 0.46
De Ridder 2006 1 4 1 66 16.50 [0.86, 315.19] 0.19
Dubinsky 2000 1 7 12 72 0.86 [0.10, 7.60] 3.09
Gazouli 2010 4 16 3 74 6.17 [1.26, 30.29] 1.68
Hawwa 2008 0 4 3 28 0.21 [0.00, 81.03] 1.46
Hindorf 2006 2 6 8 44 1.83 [0.31, 10.75] 2.71
Hlavaty 2013 11 4 21 184 24.10 [7.04, 82.45] 1.29
Mazor 2013 0 4 24 148 0.03 [0.00, 15586.61] 1.91
Naughton 1999 1 0 1 13 115.31 [0.04, 3.3e+05] 0.03
Stocco 2004 0 4 13 27 0.04 [0.00, 32.90] 4.19
Stocco 2005 0 5 7 58 0.10 [0.00, 175.09] 1.89
Stocco 2007 0 5 3 62 0.23 [0.00, 389.95] 0.94
Van Dieren 2005 3 7 9 90 4.29 [0.94, 19.52] 1.96
Winter 2007 1 10 3 116 3.87 [0.37, 40.69] 0.78
Zabala-Fernández 2011 3 4 9 90 7.50 [1.45, 38.91] 1.15
Zelinkova 2006 4 20 8 230 5.75 [1.59, 20.77] 2.07
Zhu 2019 4 9 68 330 2.16 [0.65, 7.21] 5.04
Heterogeneity: I^2 = 38.56%, H^2 = 1.63 3.70 [2.47, 5.56]
Test of $\theta_i = \theta_j$: Q(16) = 26.04, p = 0.05
White/Caucasian
Al-Judaibi 2016 2 3 5 43 5.73 [0.76, 42.99] 0.96
Gearry 2003 2 7 0 91 29.77 [2.26, 391.90] 0.21
Larussa 2012 1 3 2 21 3.50 [0.24, 51.46] 0.75
Mhanna 2019 4 3 2 140 93.33 [12.05, 722.62] 0.14
Marinaki 2004 1 7 10 61 0.87 [0.10, 7.86] 3.00
Palmieri 2007 6 21 17 376 6.32 [2.26, 17.69] 2.88
Reuther 2003 0 4 0 62 1.00 [0.00, 3925.66] 0.19
Ribaldone 2019 0 8 6 186 0.13 [0.00, 2541.91] 0.94
Schwab 2002 3 5 2 83 24.90 [3.36, 184.71] 0.36
Steponaitiene 2016 9 0 8 65 615.16 [1.54, 2.5e+05] 0.04
Wroblova 2012 8 8 26 146 5.62 [1.94, 16.29] 3.75
Heterogeneity: I^2 = 36.23%, H^2 = 1.57 7.77 [4.76, 12.68]
Test of $\theta_i = \theta_j$: Q(10) = 15.68, p = 0.11
Overall 3.18 [2.49, 4.06]
Heterogeneity: I^2 = 52.18%, H^2 = 2.09
Test of $\theta_i = \theta_j$: Q(39) = 81.56, p = 0.00
Higher in non-mut
Higher in mut
Test of group differences: $Q_b(2)$ = 20.80, p = 0.00
1/64
1/4
4
64
Fixed-effects Mantel-Haenszel model

Figure S30. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Total hematologic adverse events. Subgroup analysis according to race

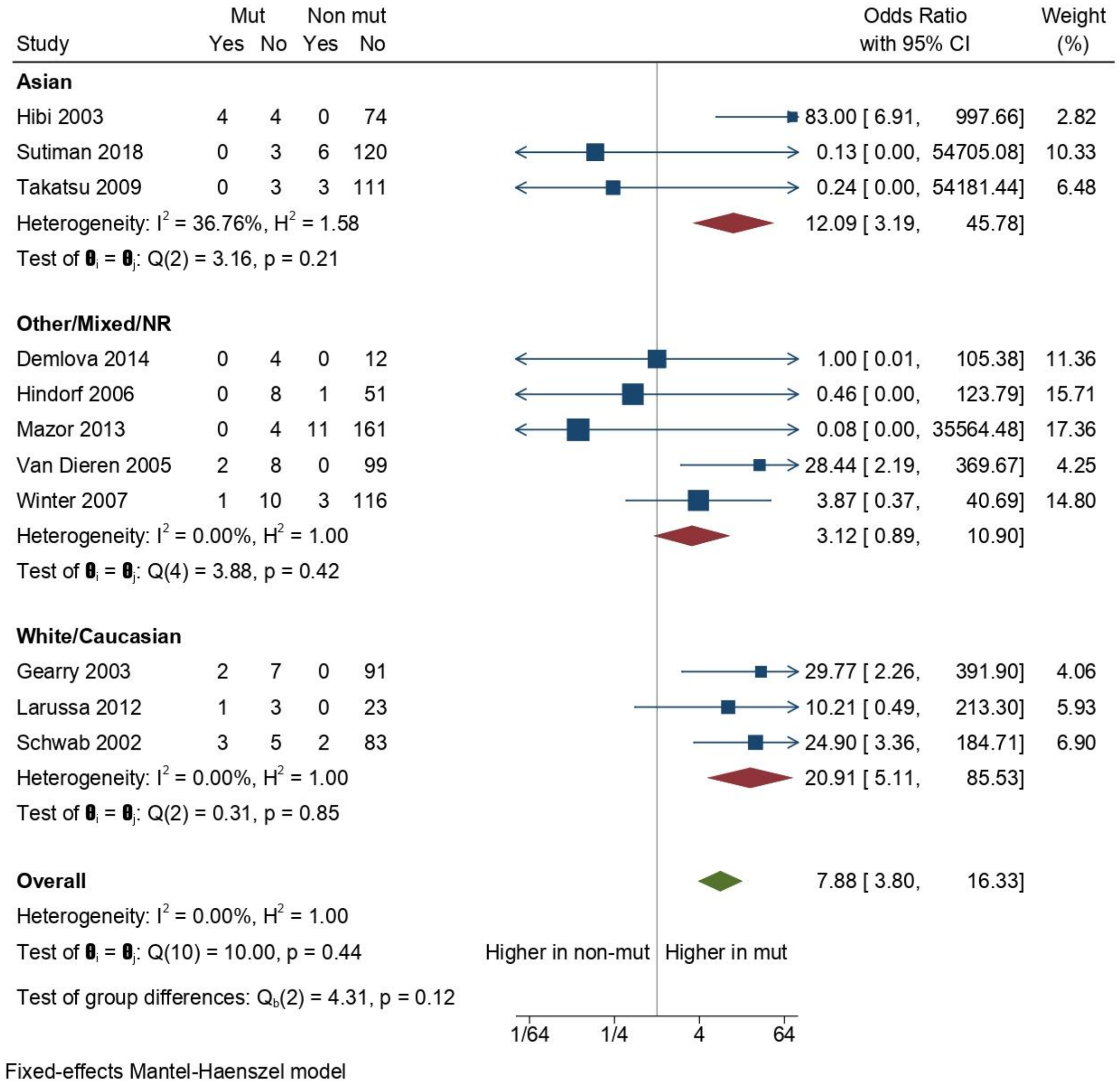


Figure S31. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Serious hematologic adverse events. Subgroup analysis according to race

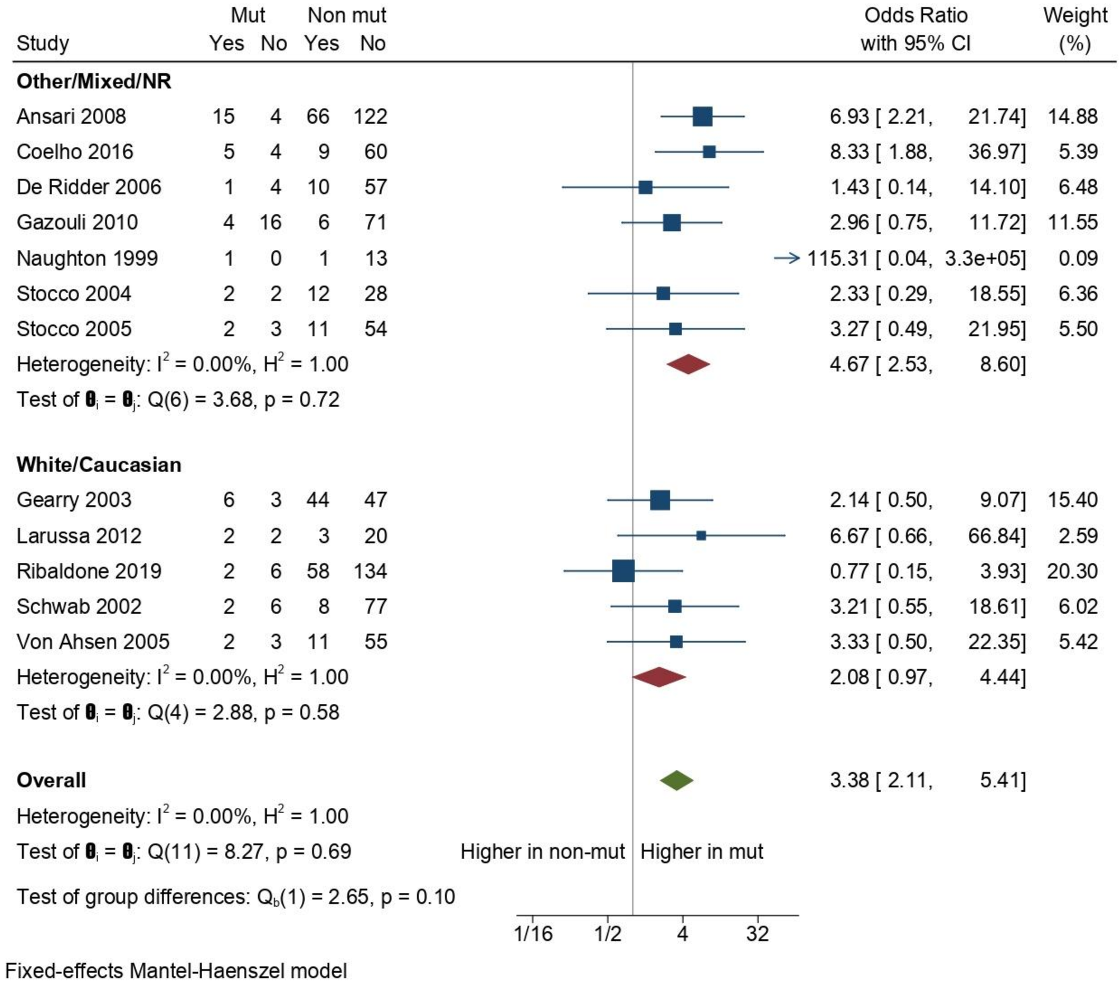


Figure S32. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Withdrawal due to adverse events. Subgroup analysis according to race

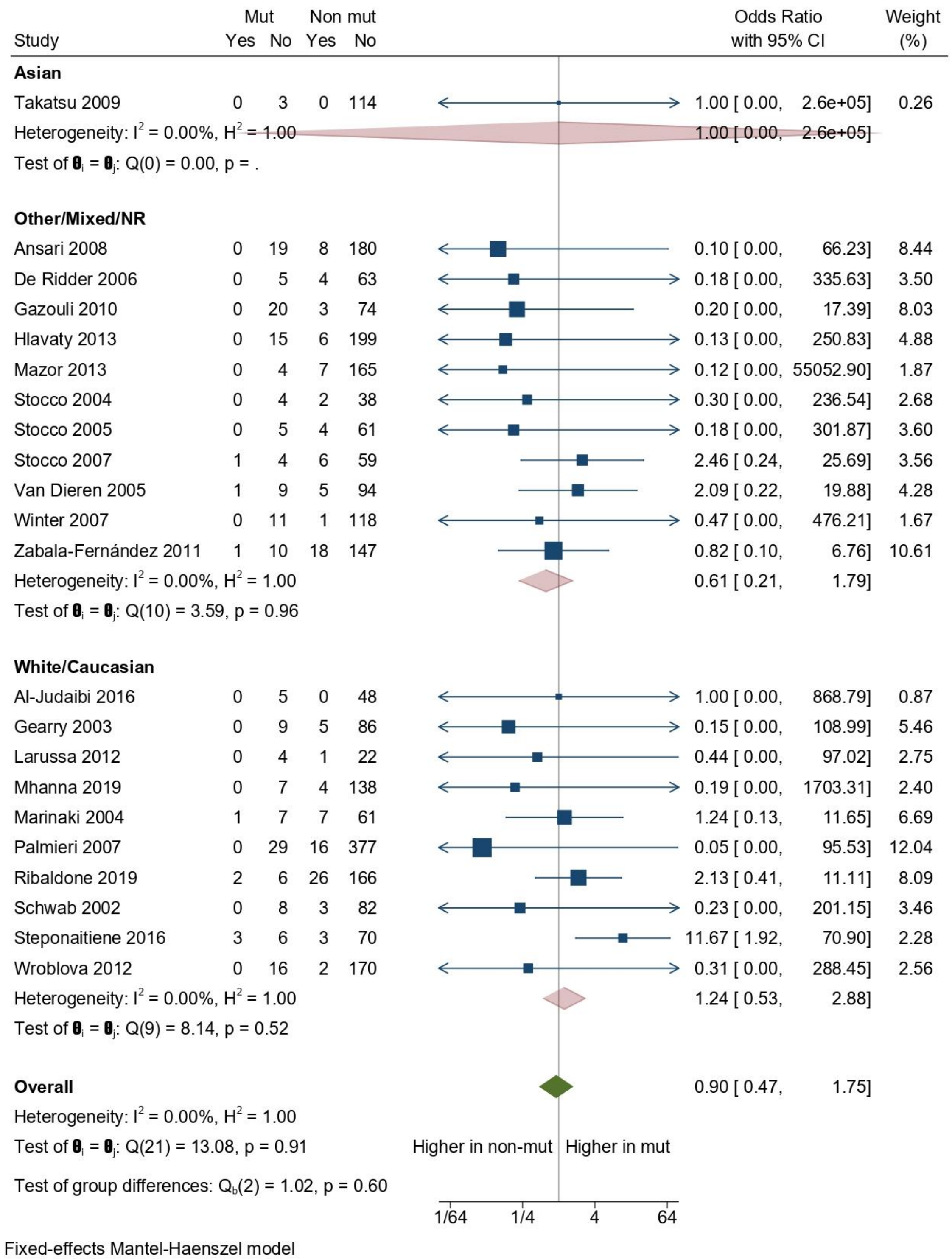


Figure S33. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Pancreatitis. Subgroup analysis according to race

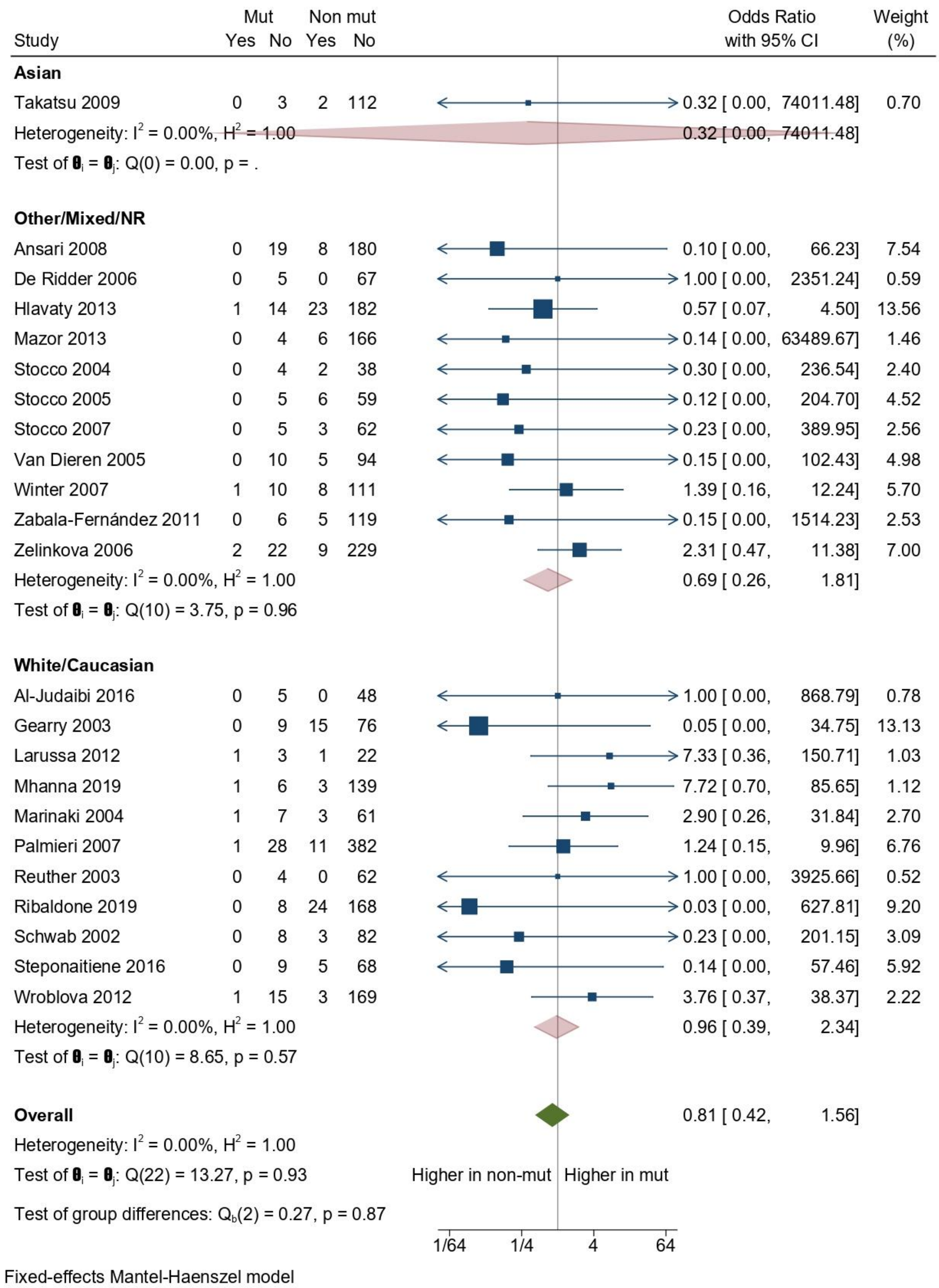


Figure S34. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Hepatotoxicity. Subgroup analysis according to race

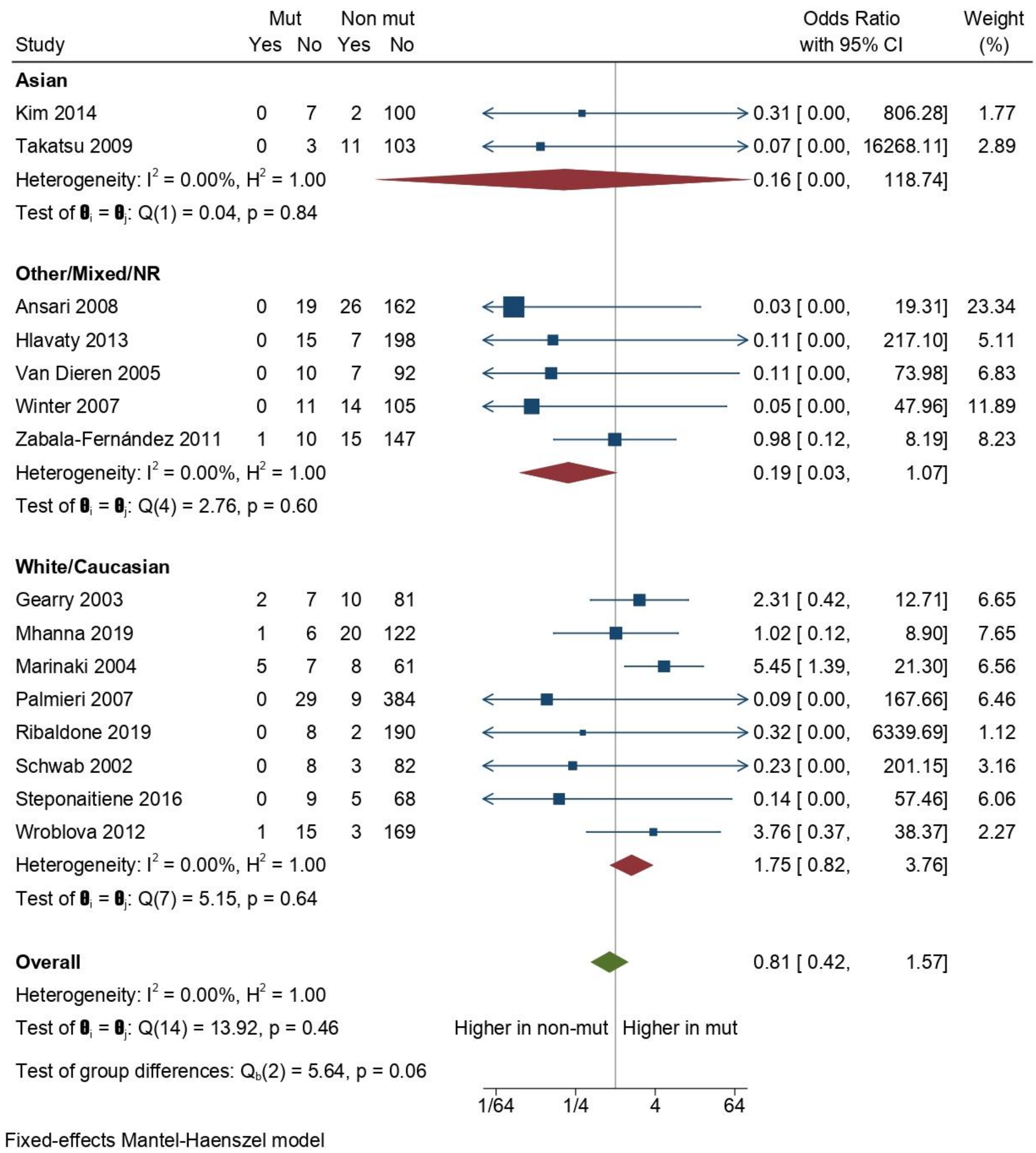


Figure S35. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Gastrointestinal side effects. Subgroup analysis according to race

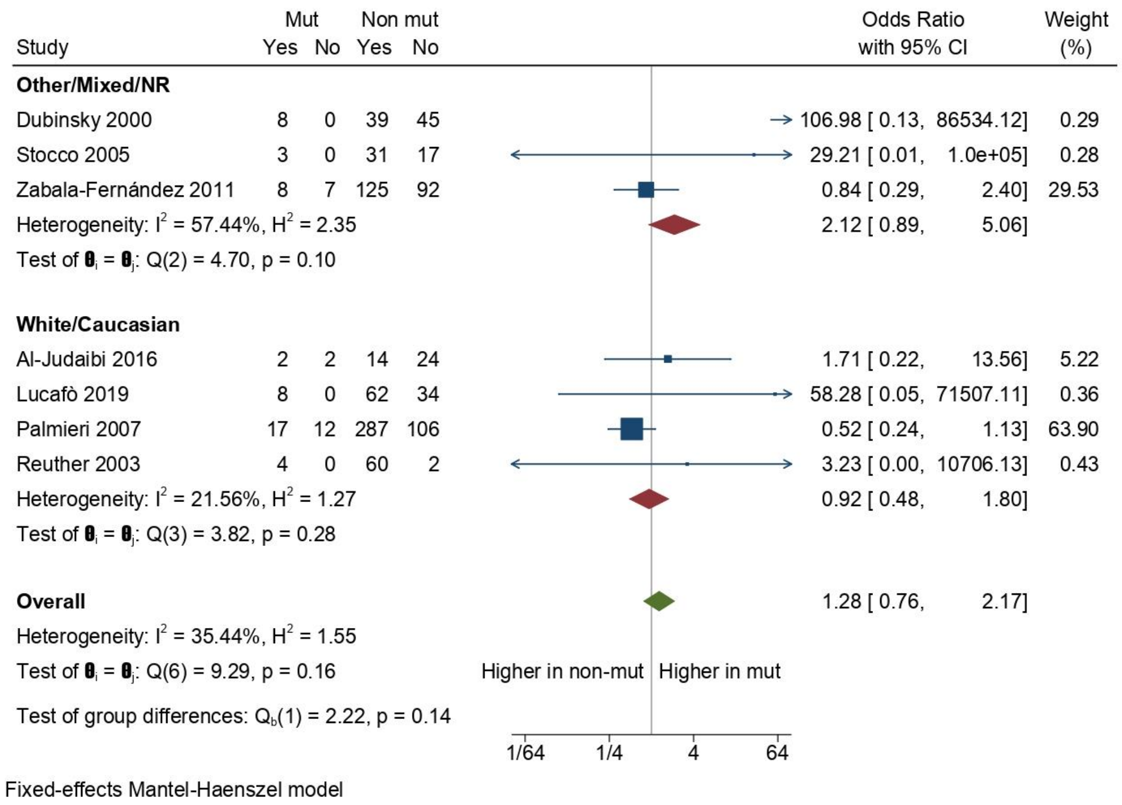


Figure S36. Forest plot of comparison mutated *TPMT* vs wild-type *TPMT*, outcome: Clinical remission. Subgroup analysis according to race

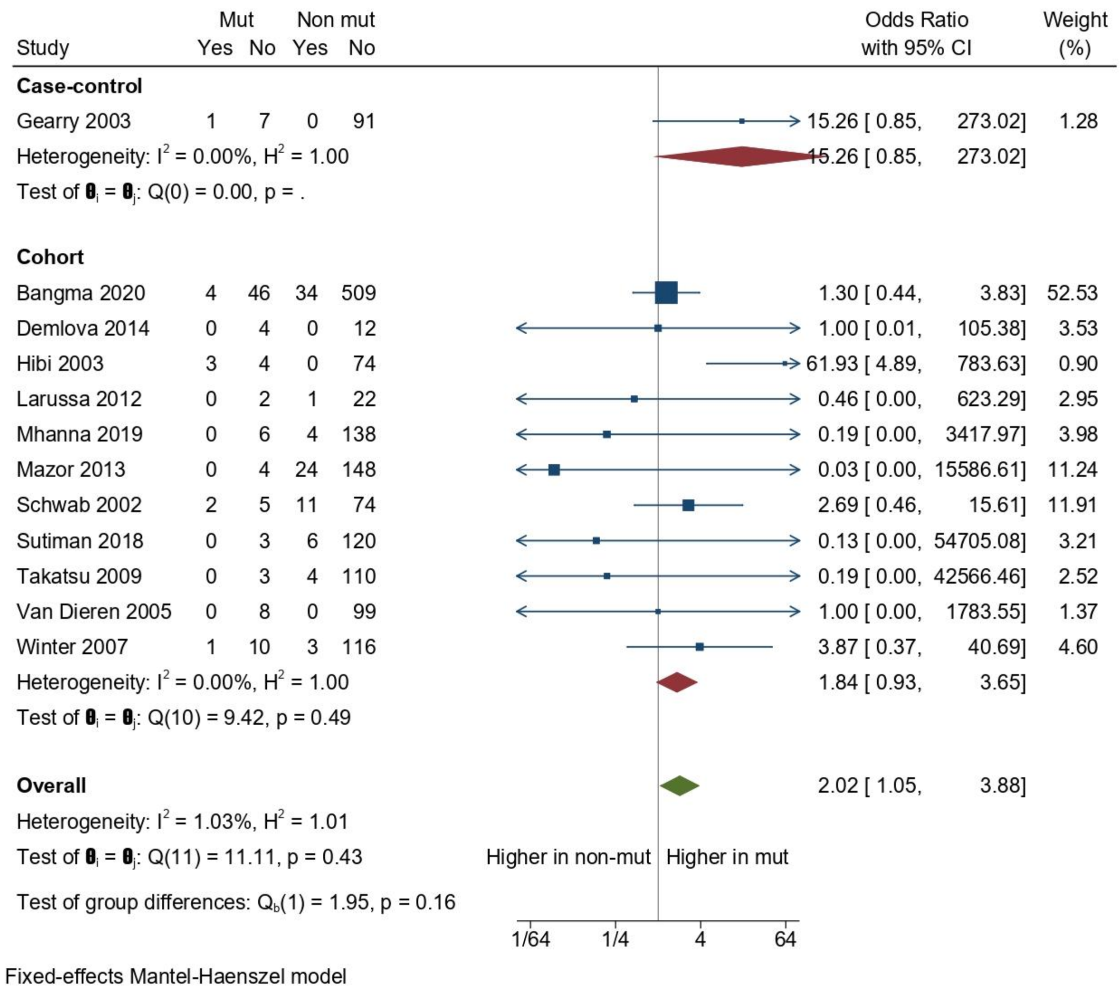
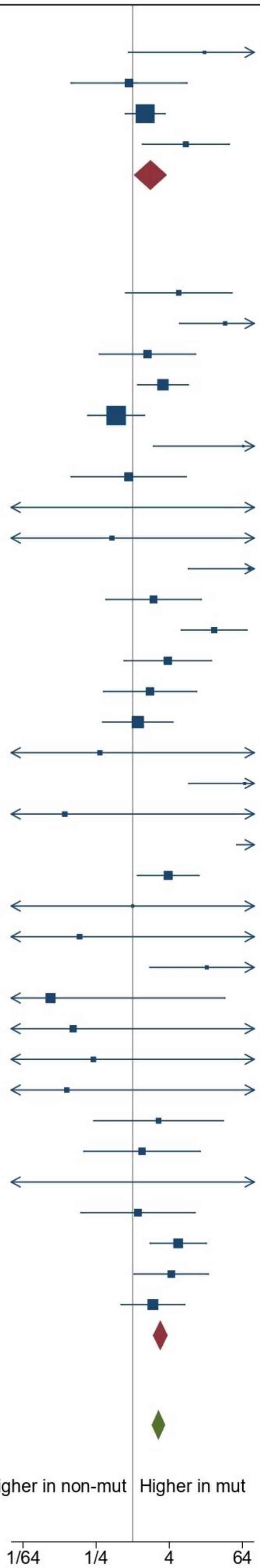


Figure S37. Forest plot of comparison heterozygous *TPMT* vs wild-type *TPMT*, outcome: Total serious adverse events

Study	Mut Yes	Mut No	Non mut Yes	Non mut No	Odds Ratio with 95% CI	Weight (%)
Case-control						
Gearry 2003	1	7	0	91	15.26 [0.85, 273.02]	0.22
Marinaki 2004	1	7	10	61	0.87 [0.10, 7.86]	3.00
Yang 2014	13	15	333	617	1.61 [0.76, 3.42]	17.31
Zabala-Fernández 2011	3	4	9	90	7.50 [1.45, 38.91]	1.15
Heterogeneity: I^2 = 43.32%, H^2 = 1.76					1.95 [1.04, 3.66]	
Test of $\theta_i = \theta_j$: Q(3) = 5.29, p = 0.15						
Cohort						
Al-Judaibi 2016	2	3	5	43	5.73 [0.76, 42.99]	0.96
Ansari 2008	5	14	2	186	33.21 [5.90, 186.87]	0.46
Asada 2016	2	3	43	113	1.75 [0.28, 10.85]	2.72
Bangma 2020	6	36	23	434	3.14 [1.20, 8.22]	5.62
Chao 2017	4	23	173	532	0.53 [0.18, 1.57]	18.42
De Ridder 2006	1	1	1	66	66.00 [2.20, 1984.21]	0.05
Dubinsky 2000	1	7	12	72	0.86 [0.10, 7.60]	3.09
Fangbin 2016	2	0	24	106	569.50 [0.00, 5.0e+09]	0.01
Hawwa 2008	0	4	1	30	0.45 [0.00, 194.65]	0.71
Hibi 2003	6	1	5	69	82.80 [8.27, 828.68]	0.21
Hindorf 2006	2	5	8	44	2.20 [0.36, 13.37]	2.30
Hlavaty 2013	10	4	21	184	21.90 [6.31, 76.02]	1.30
Kim 2010	5	2	111	168	3.78 [0.72, 19.85]	2.63
Kim 2014	2	4	21	81	1.93 [0.33, 11.25]	2.64
Kim 2017	4	5	128	194	1.21 [0.32, 4.60]	6.55
Larussa 2012	0	2	2	21	0.29 [0.00, 373.91]	0.76
Mhanna 2019	3	3	2	140	70.00 [8.37, 585.21]	0.14
Mazor 2013	0	4	11	161	0.08 [0.00, 35564.48]	0.92
Naughton 1999	1	0	1	13	115.31 [0.04, 3.3e+05]	0.03
Palmieri 2007	4	23	17	376	3.85 [1.20, 12.37]	3.16
Reuther 2003	0	4	0	62	1.00 [0.00, 3925.66]	0.19
Ribaldone 2019	0	8	6	186	0.13 [0.00, 2541.91]	0.94
Schwab 2002	2	5	2	83	16.60 [1.92, 143.62]	0.37
Stocco 2004	0	4	13	27	0.04 [0.00, 32.90]	4.19
Stocco 2005	0	5	7	58	0.10 [0.00, 175.09]	1.89
Stocco 2007	0	5	3	62	0.23 [0.00, 389.95]	0.94
Sutiman 2018	0	3	10	116	0.08 [0.00, 33361.89]	0.86
Takatsu 2009	1	2	18	96	2.67 [0.23, 30.99]	1.04
Van Dieren 2005	1	7	9	90	1.43 [0.16, 12.95]	2.00
Wang 2018	1	0	18	61	264.44 [0.00, 1.2e+10]	0.01
Winter 2007	1	10	9	110	1.22 [0.14, 10.65]	2.35
Wroblova 2012	8	8	26	146	5.62 [1.94, 16.29]	3.75
Zelinkova 2006	3	20	8	230	4.31 [1.06, 17.55]	2.08
Zhu 2019	4	9	68	330	2.16 [0.65, 7.21]	5.05
Heterogeneity: I^2 = 47.96%, H^2 = 1.92					2.84 [2.15, 3.77]	
Test of $\theta_i = \theta_j$: Q(33) = 63.42, p = 0.00						
Overall					2.65 [2.05, 3.43]	
Heterogeneity: I^2 = 47.46%, H^2 = 1.90						
Test of $\theta_i = \theta_j$: Q(37) = 70.42, p = 0.00						
Test of group differences: $Q_b(1)$ = 1.14, p = 0.29						



Fixed-effects Mantel-Haenszel model

Figure S38. Forest plot of comparison heterozygous *TPMT* vs wild-type *TPMT*, outcome: Total hematologic adverse events

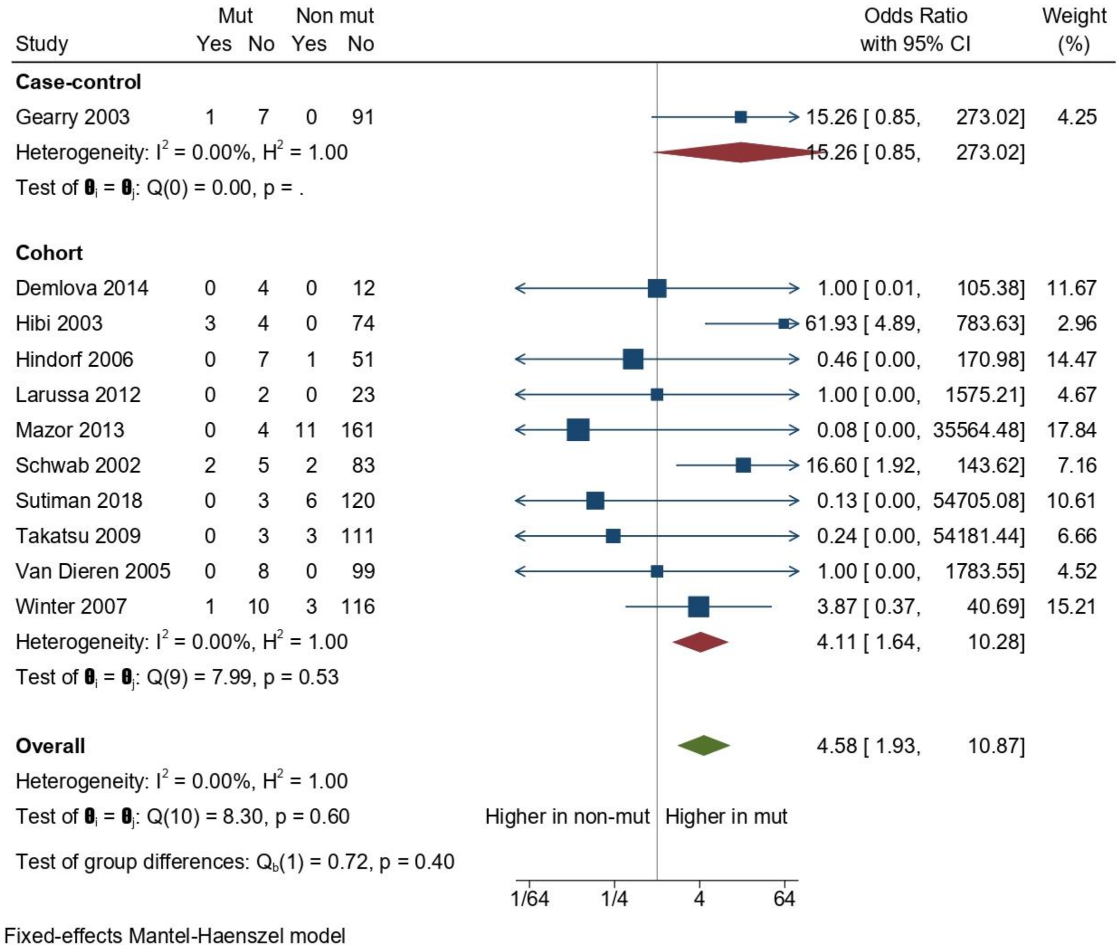


Figure S39. Forest plot of comparison heterozygous *TPMT* vs wild-type *TPMT*, outcome: Serious hematologic adverse events

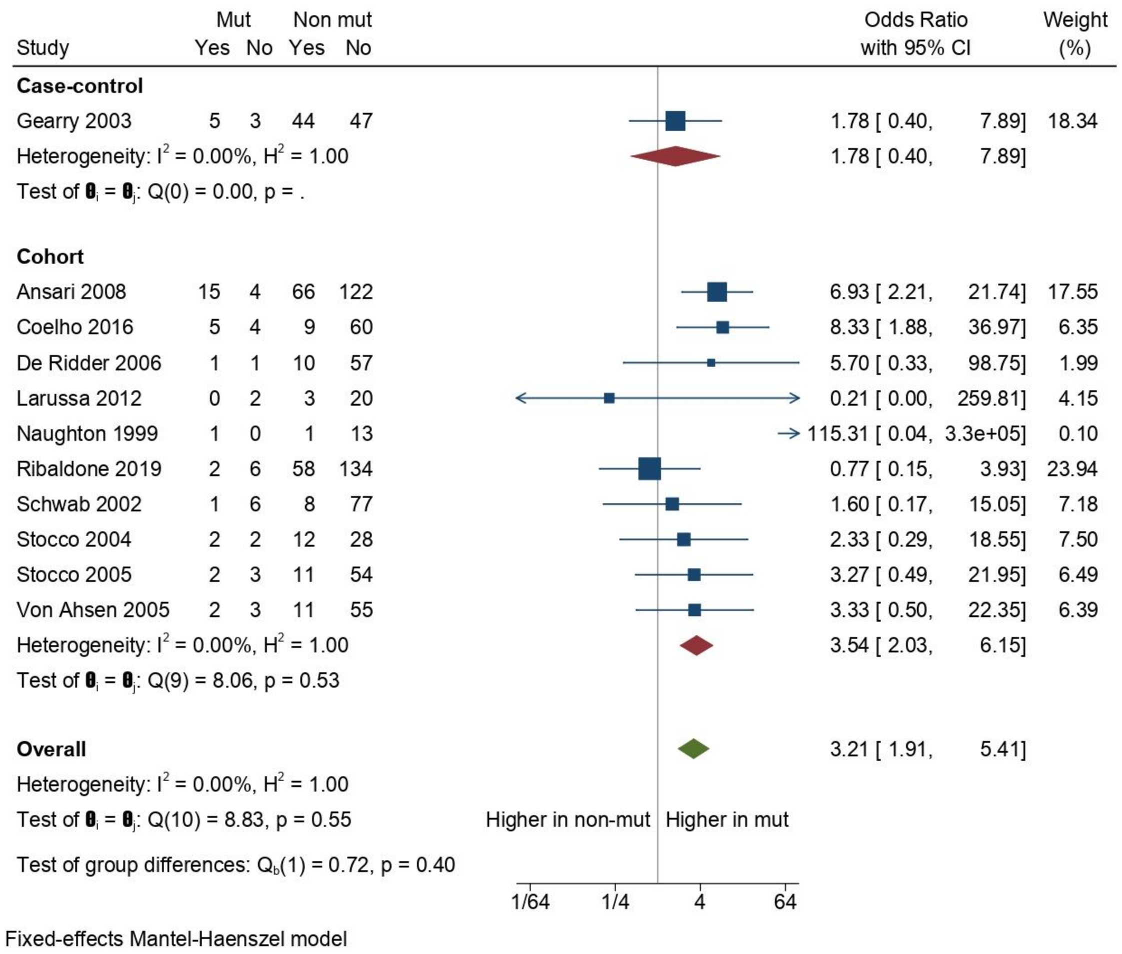


Figure S40. Forest plot of comparison heterozygous *TPMT* vs wild-type *TPMT*, outcome: Withdrawal due to AE

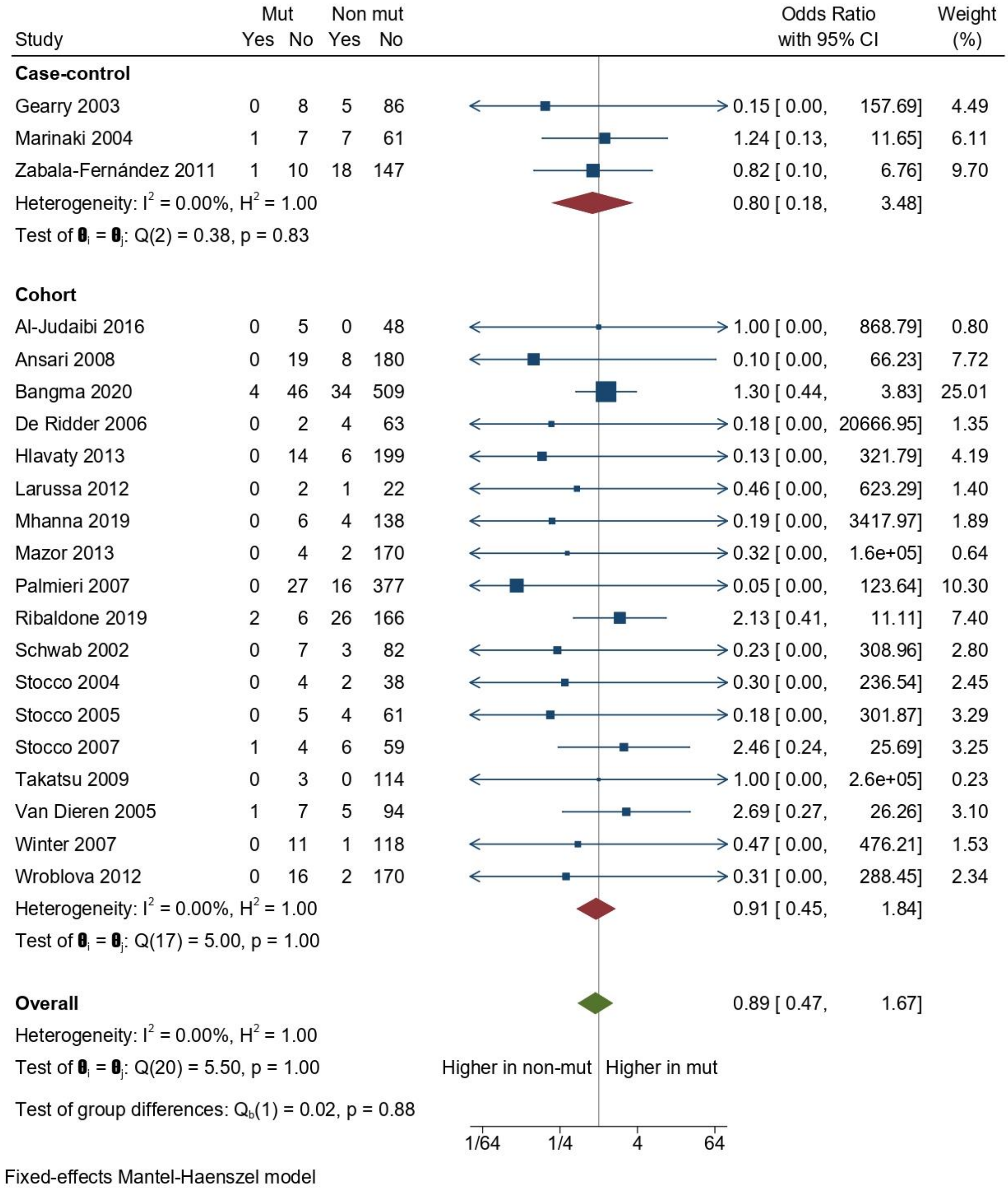


Figure S41. Forest plot of comparison heterozygous *TPMT* vs wild-type *TPMT*, outcome: Pancreatitis

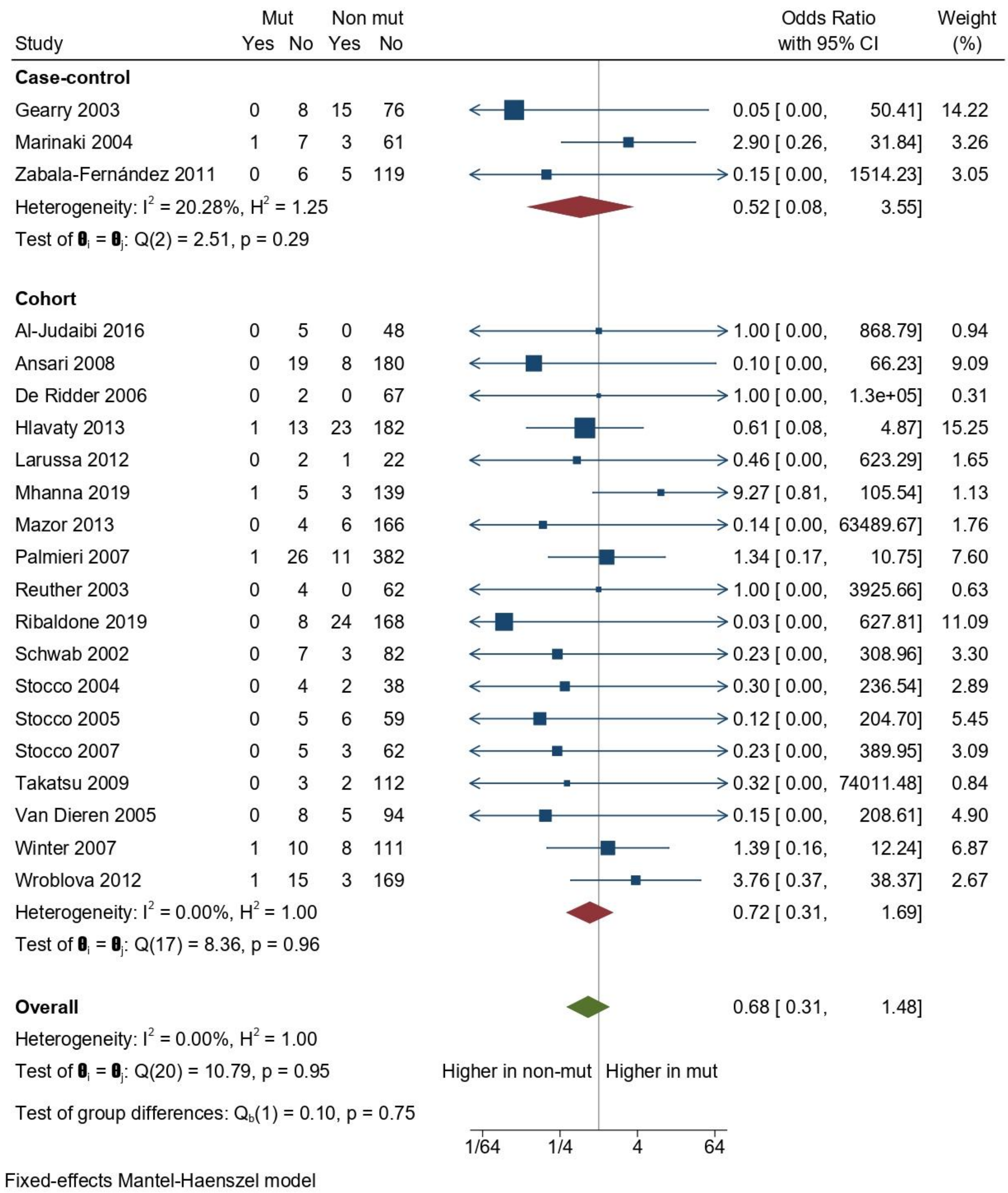


Figure S42. Forest plot of comparison heterozygous *TPMT* vs wild-type *TPMT*, outcome: Hepatotoxicity

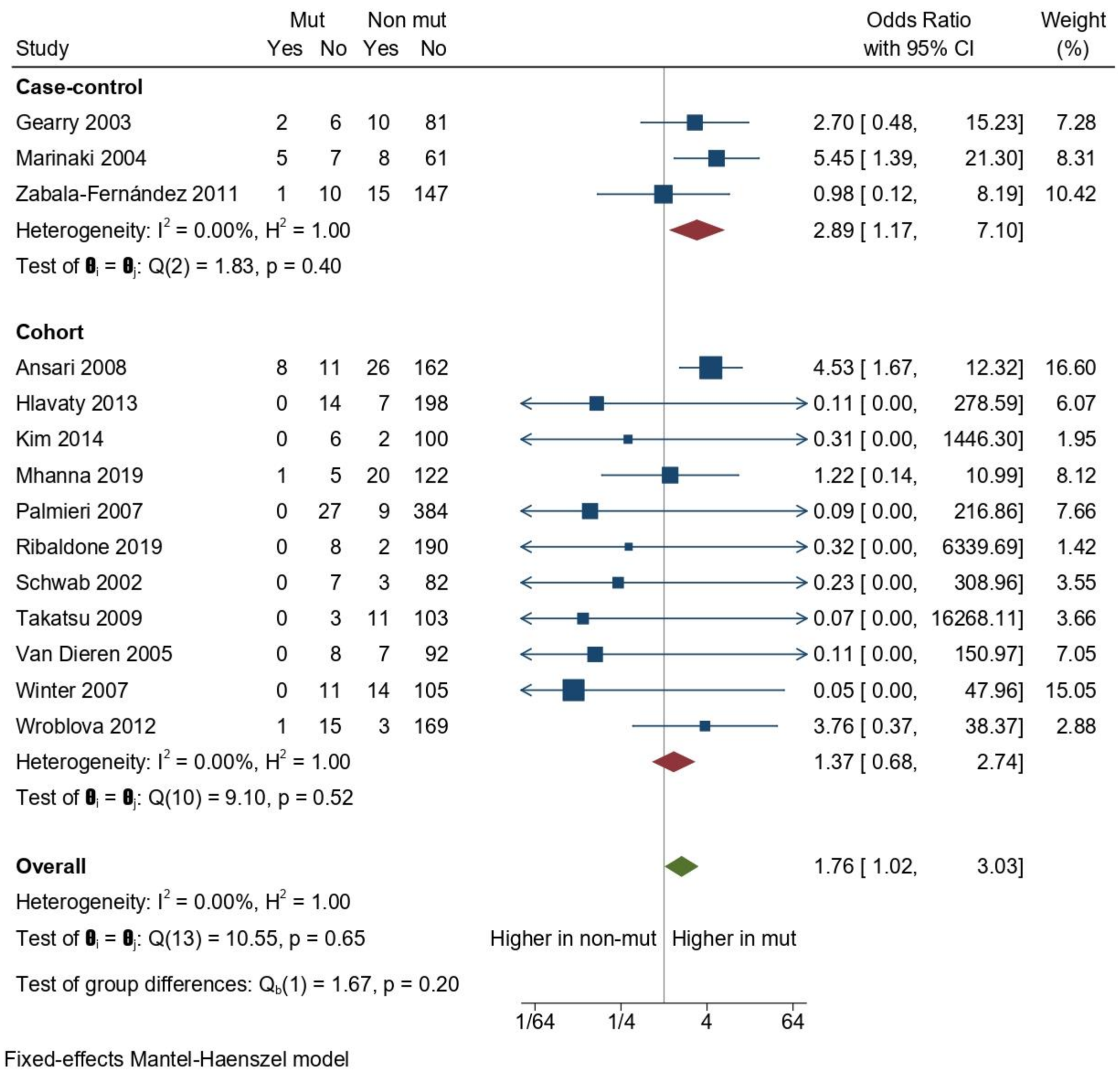


Figure S43. Forest plot of comparison heterozygous *TPMT* vs wild-type *TPMT*, outcome: Gastrointestinal side effects

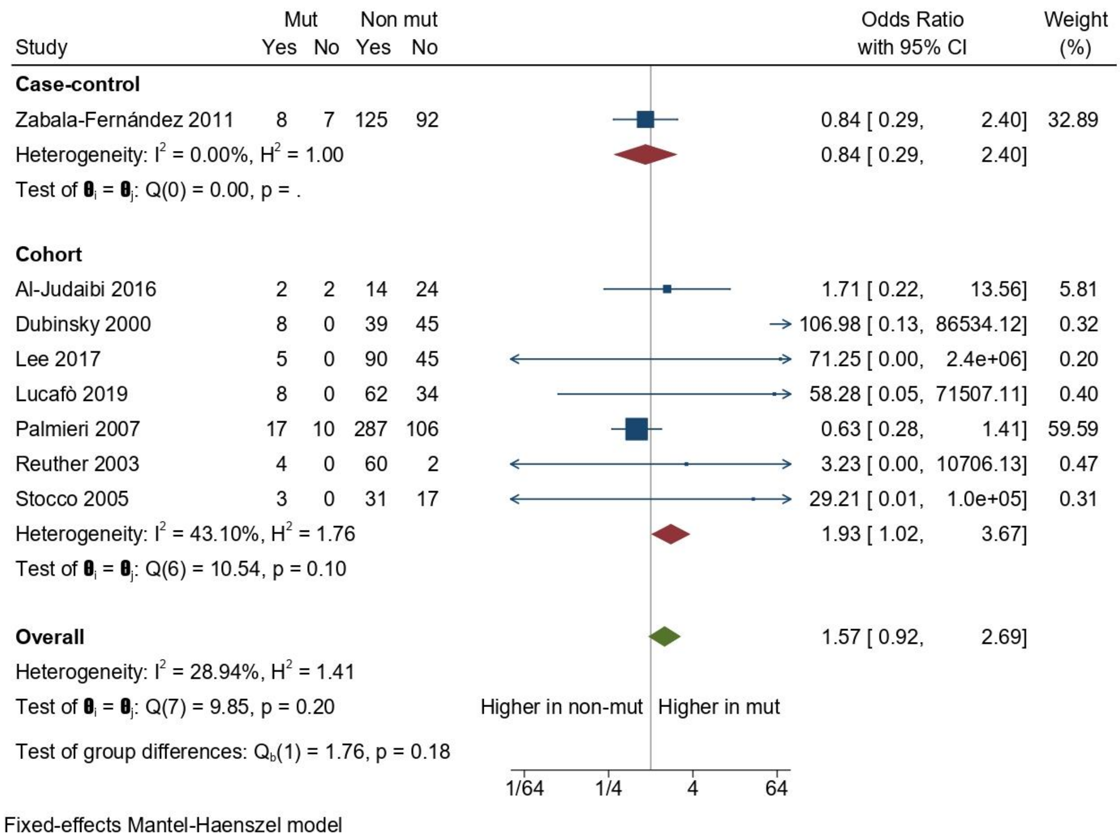


Figure S44. Forest plot of comparison heterozygous *TPMT* vs wild-type *TPMT*, outcome: Clinical remission

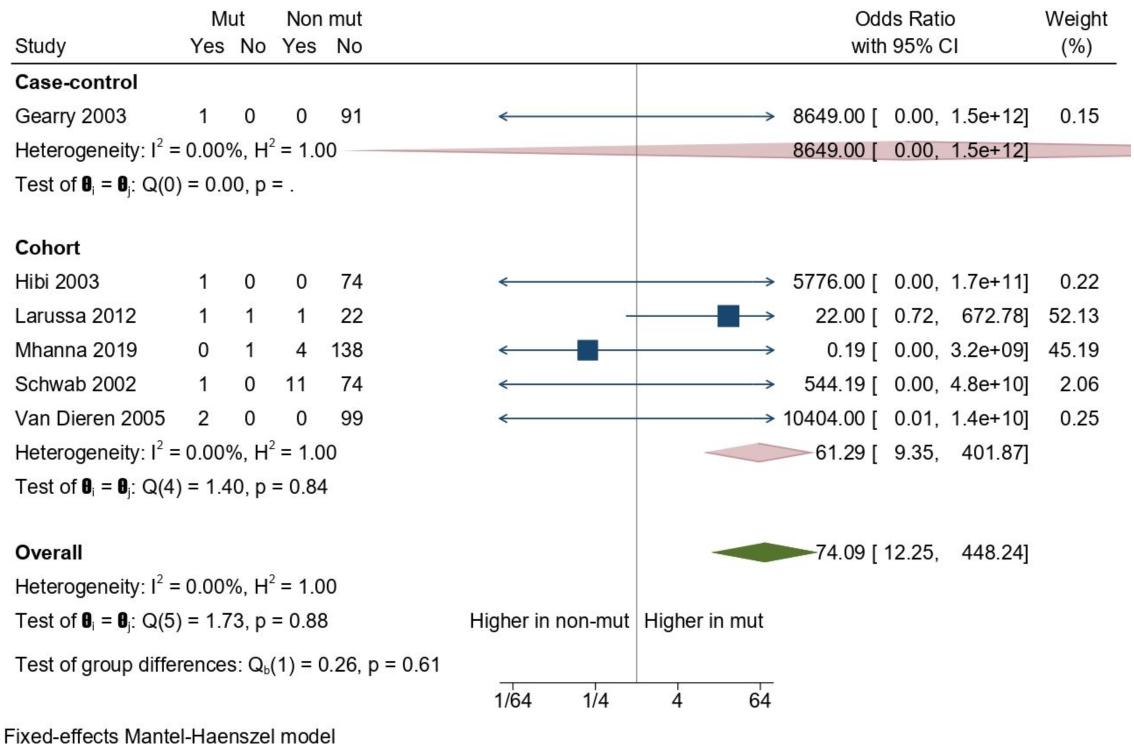


Figure S45. Forest plot of comparison 2 mutant *TPMT* alleles vs wild-type, outcome: Total serious adverse events

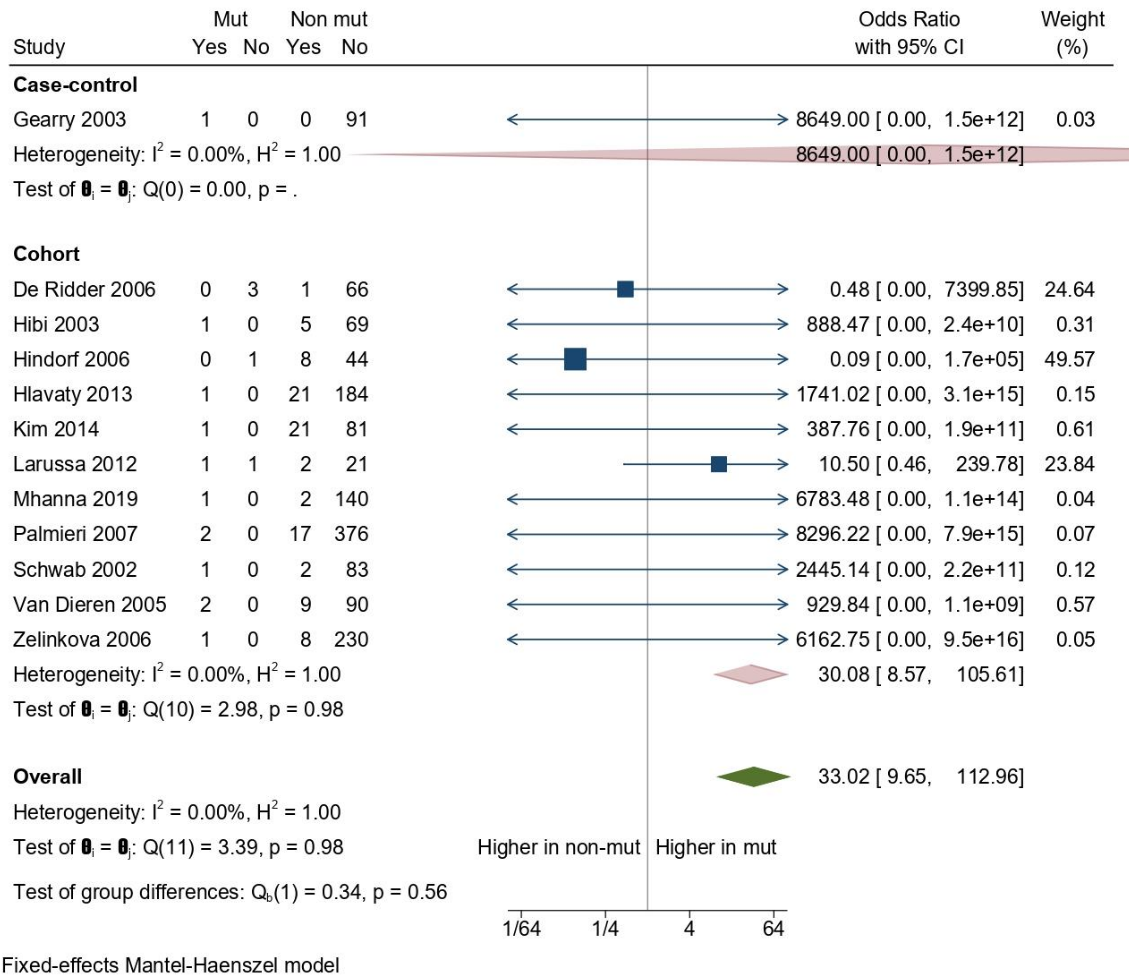


Figure S46. Forest plot of comparison 2 mutant *TPMT* alleles vs wild-type, outcome: Total hematologic adverse events

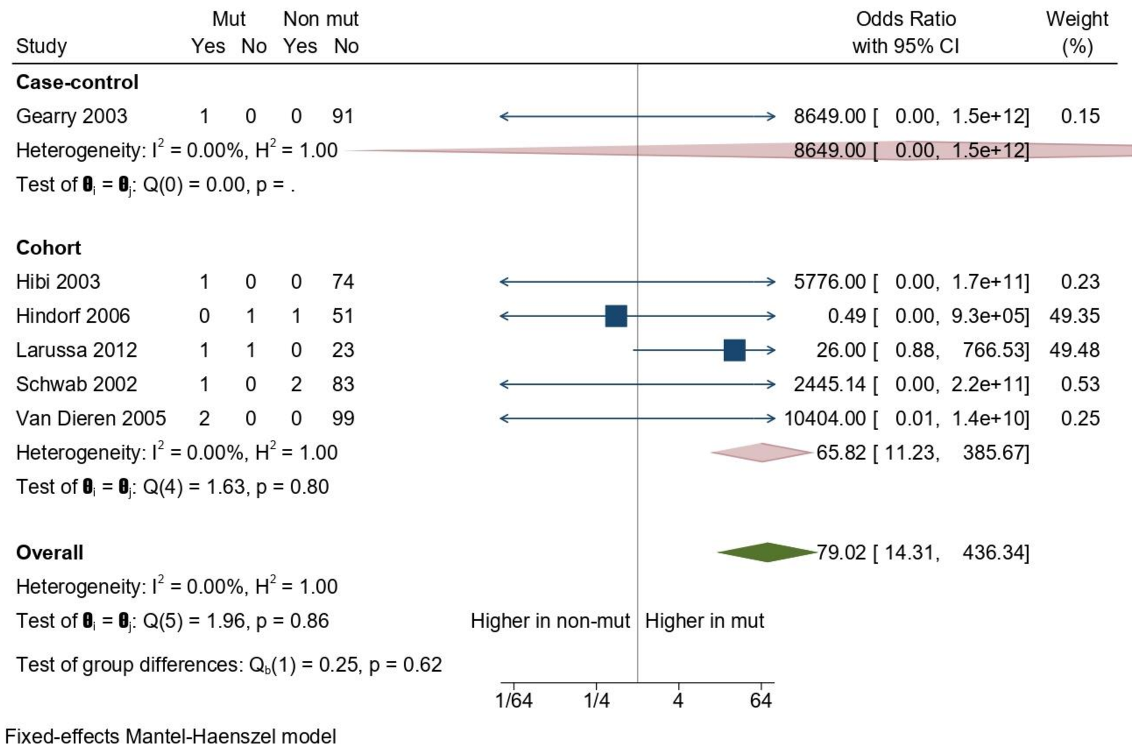


Figure S47. Forest plot of comparison 2 mutant *TPMT* alleles vs wild-type, outcome: Serious hematologic adverse events

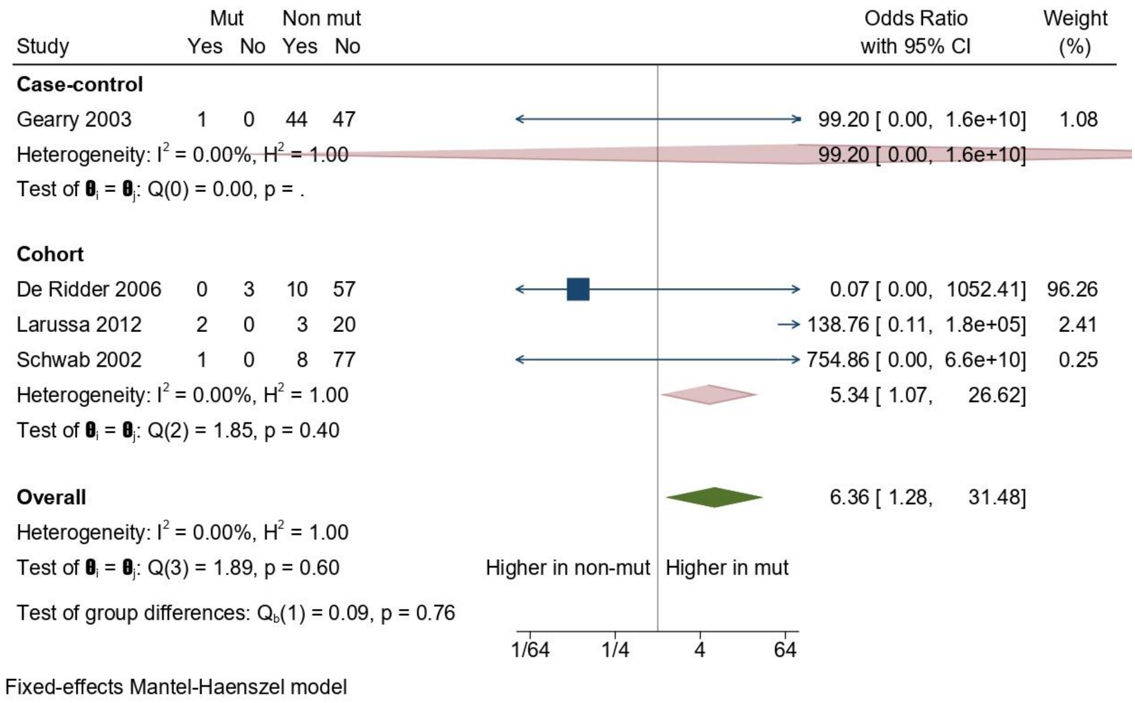


Figure S48. Forest plot of comparison 2 mutant *TPMT* alleles vs wild-type, outcome: Withdrawal due to adverse events

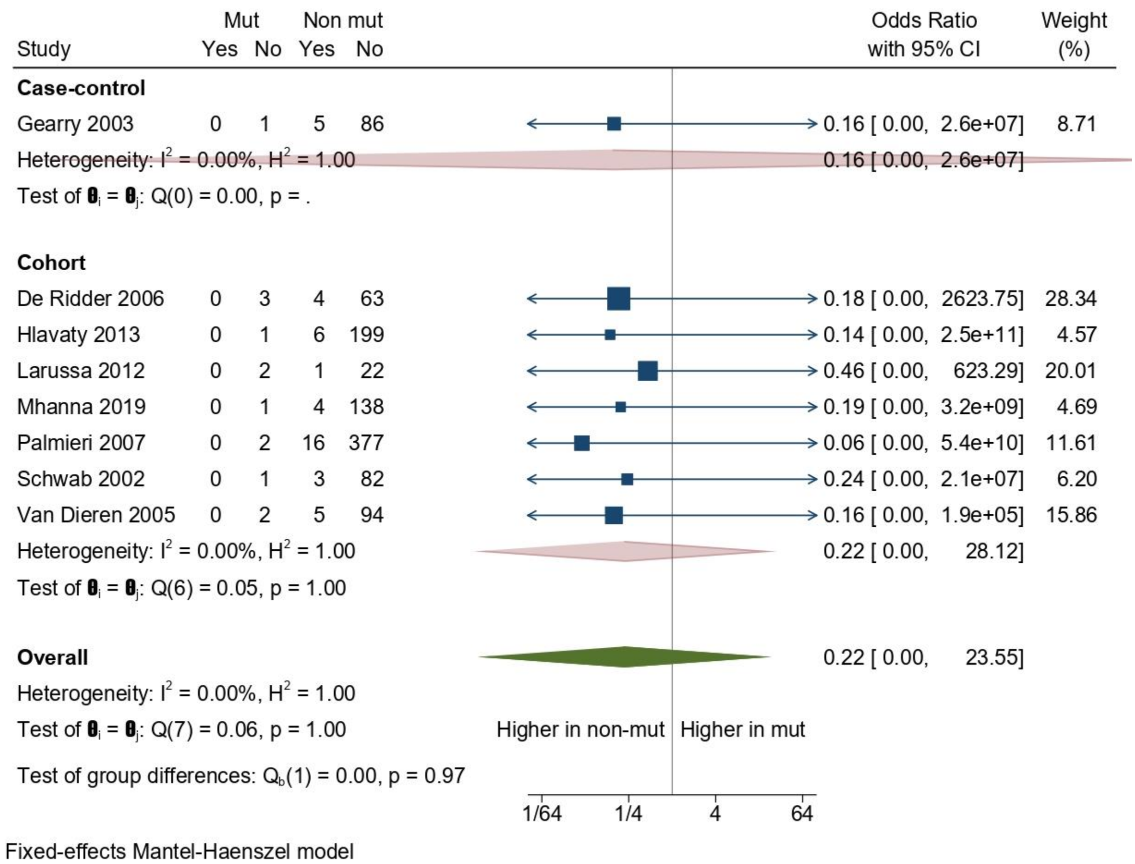


Figure S49. Forest plot of comparison 2 mutant *TPMT* alleles vs wild-type, outcome: Pancreatitis

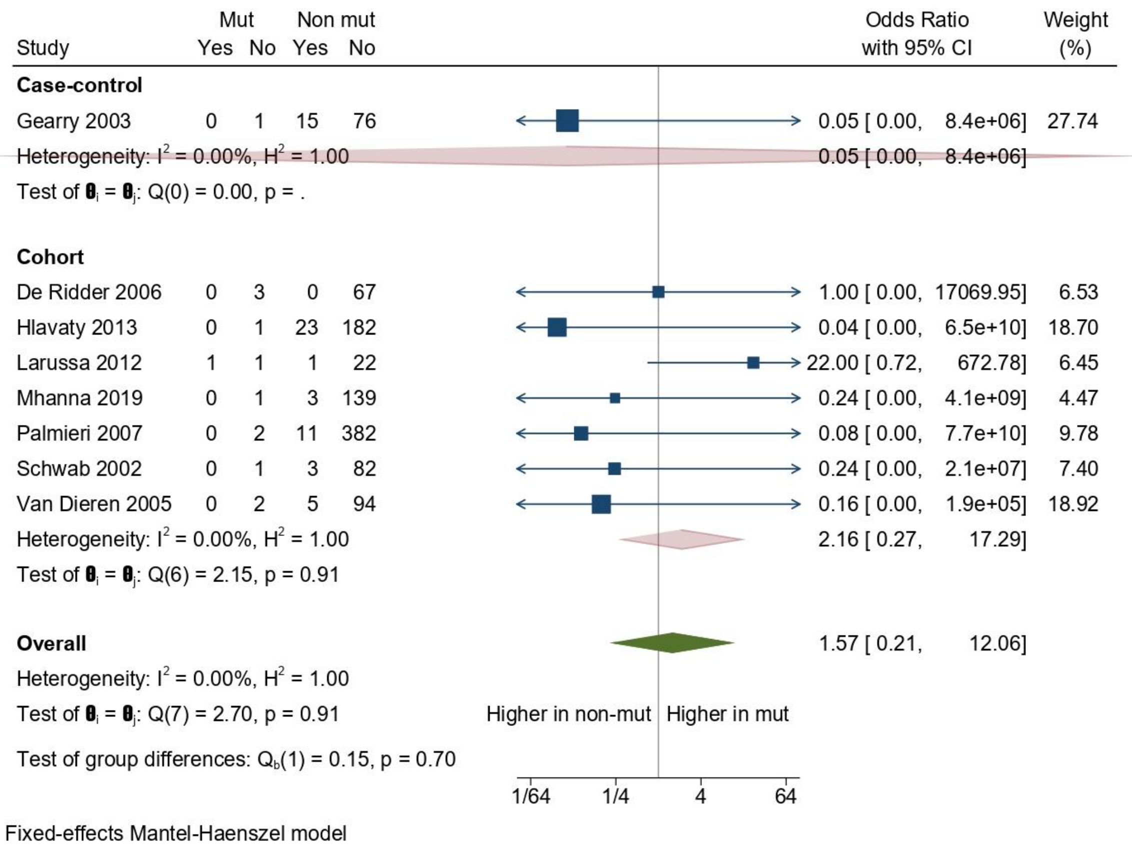


Figure S50. Forest plot of comparison 2 mutant *TPMT* alleles vs wild-type, outcome: Hepatotoxicity

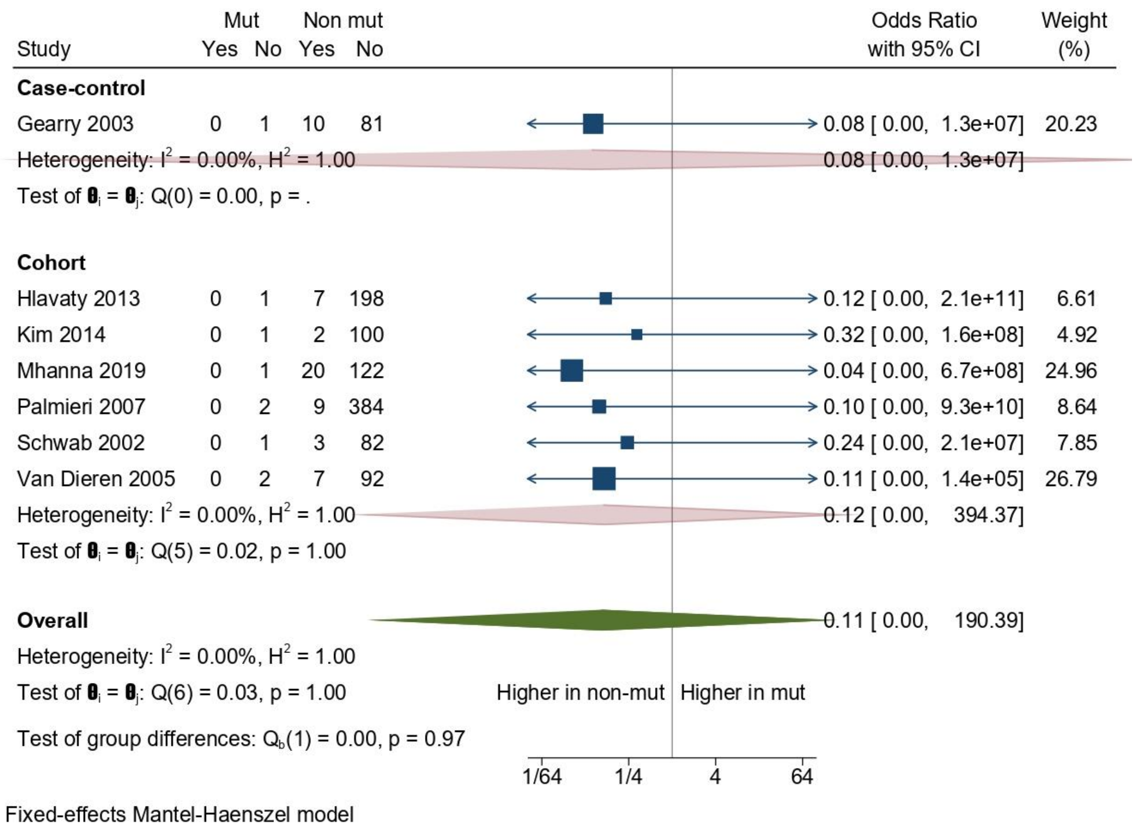


Figure S51. Forest plot of comparison 2 mutant *TPMT* alleles vs wild-type, outcome: Gastrointestinal side effects

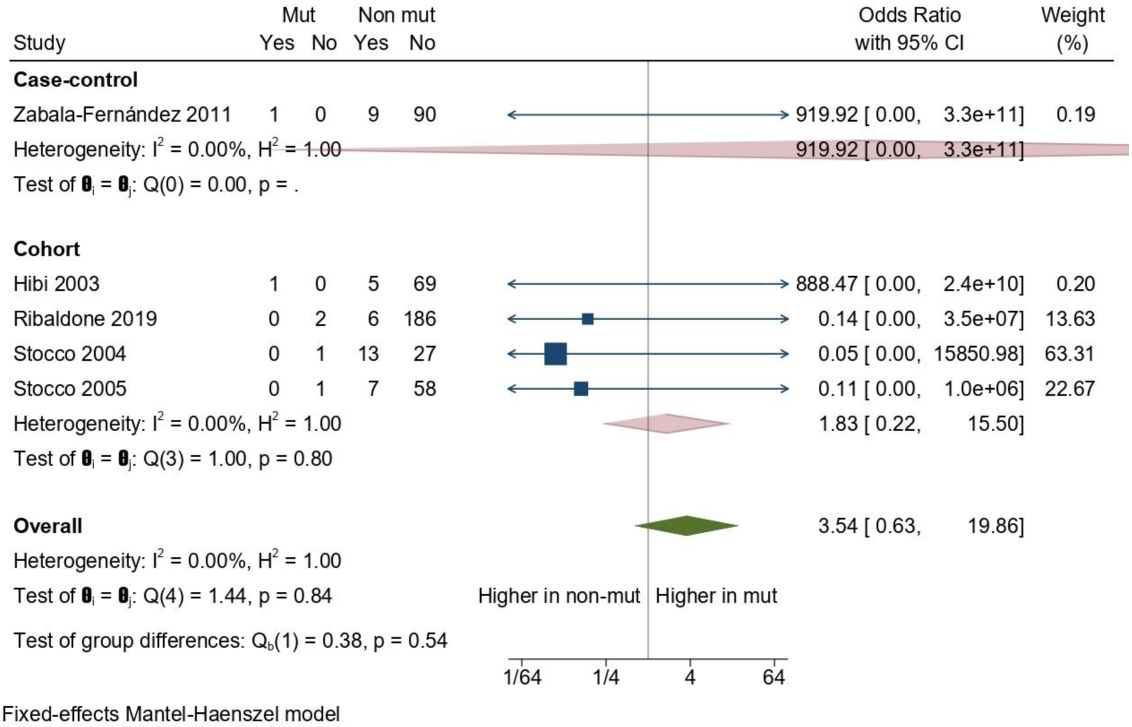


Figure S52. Forest plot of comparison *TPMT2 heterozygous vs wild-type, outcome: Total hematologic adverse events**

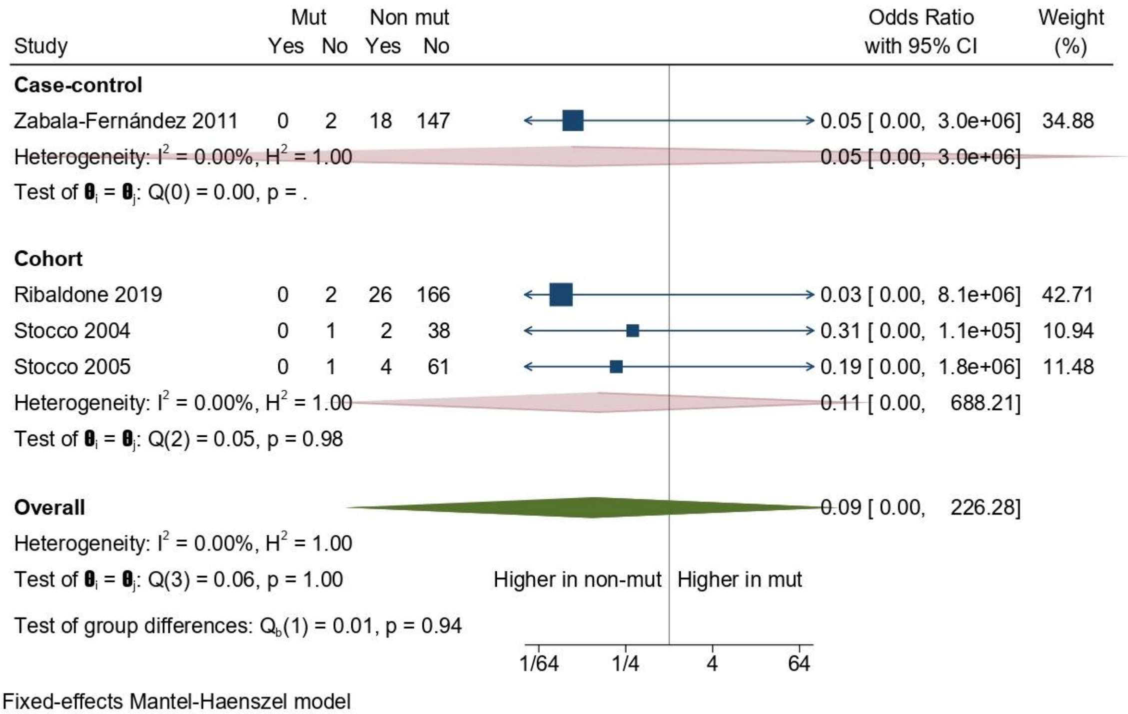


Figure S53. Forest plot of comparison *TPMT2 heterozygous vs wild-type, outcome: Pancreatitis**

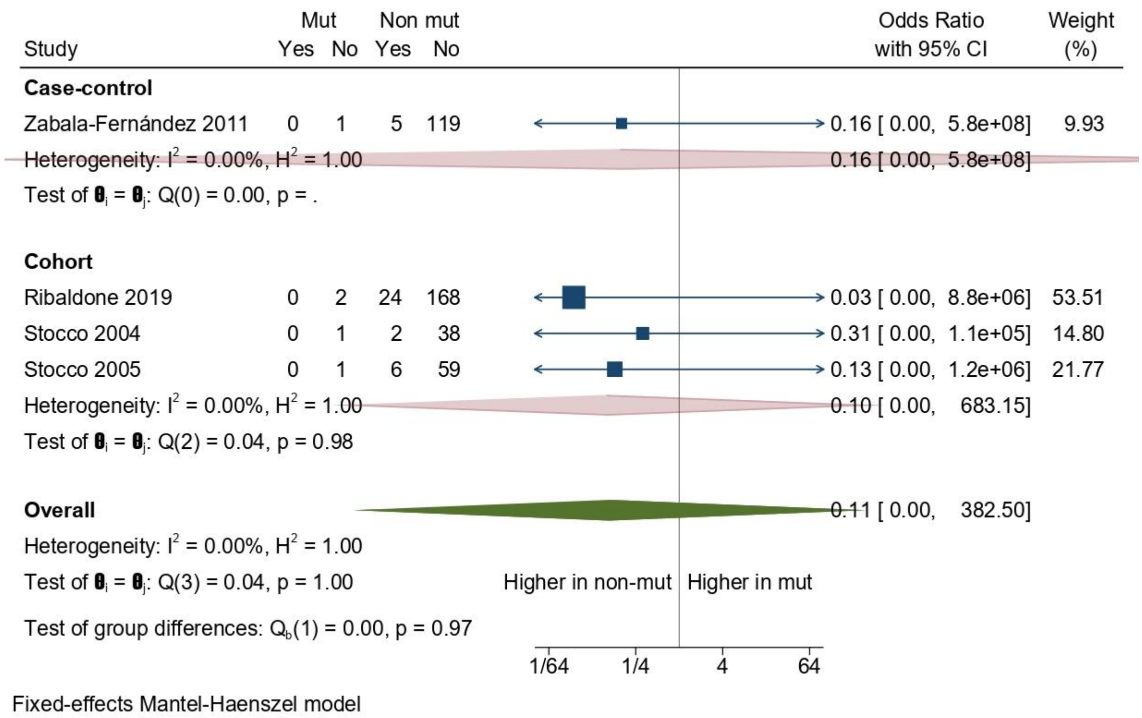


Figure S54. Forest plot of comparison *TPMT2 heterozygous vs wild-type, outcome: Hepatotoxicity**

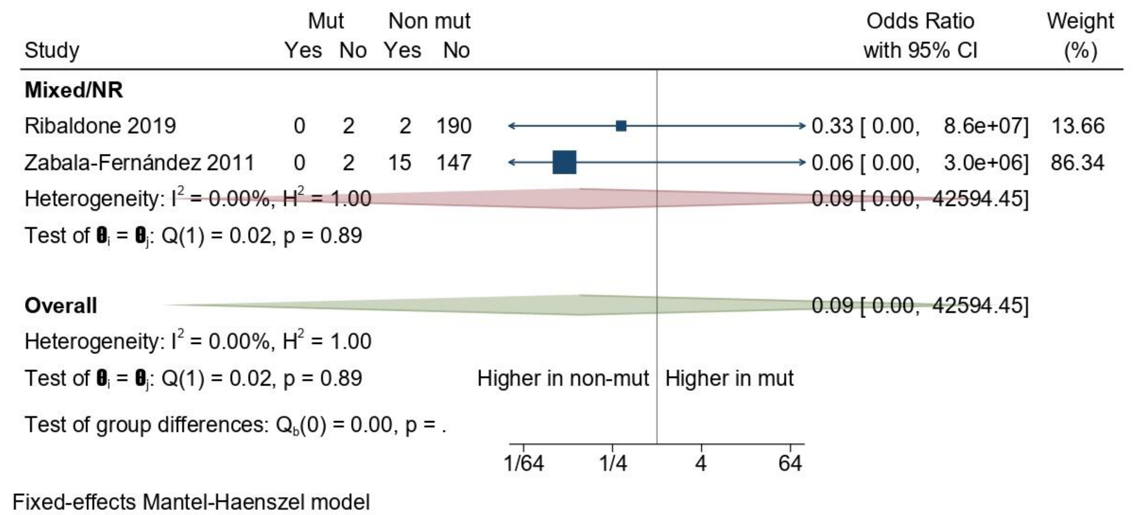


Figure S55. Forest plot of comparison *TPMT2 heterozygous vs wild-type, outcome: Gastrointestinal side effects**

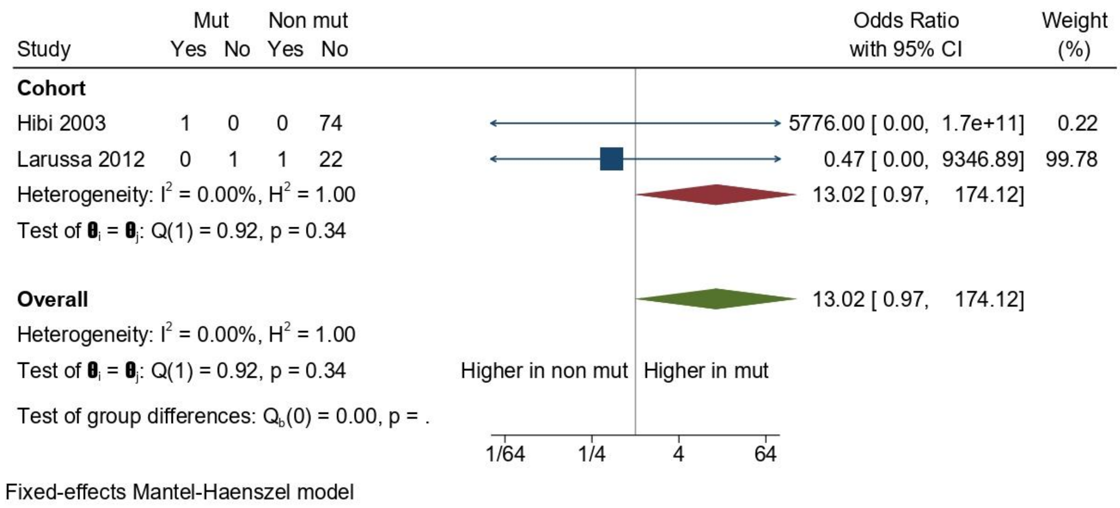


Figure S56. Forest plot of comparison *TPMT2, 2 mutant alleles vs wild-type, outcome: Total serious adverse events**

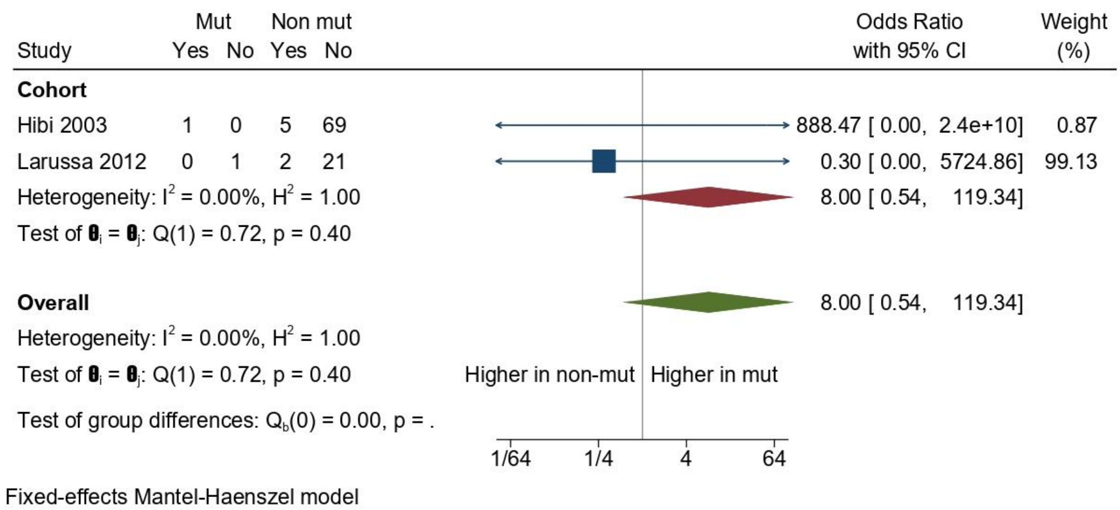


Figure S57. Forest plot of comparison *TPMT2, 2 mutant alleles vs wild-type, outcome: Total hematologic adverse events**

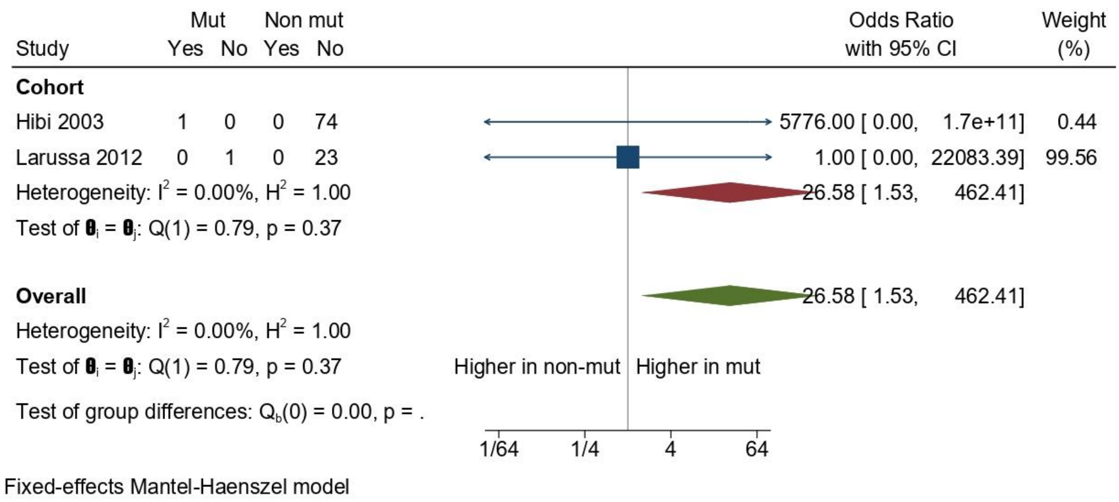


Figure S58. Forest plot of comparison *TPMT2, 2 mutant alleles vs wild-type, outcome: Serious hematologic adverse events**

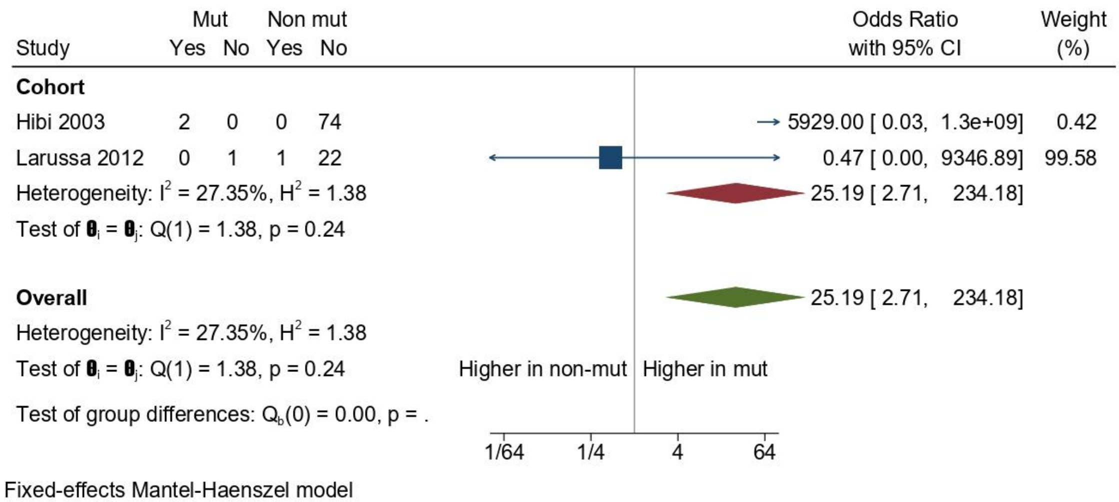


Figure S59. Forest plot of comparison mutated *TPMT2 vs wild-type, outcome: Total serious adverse events**

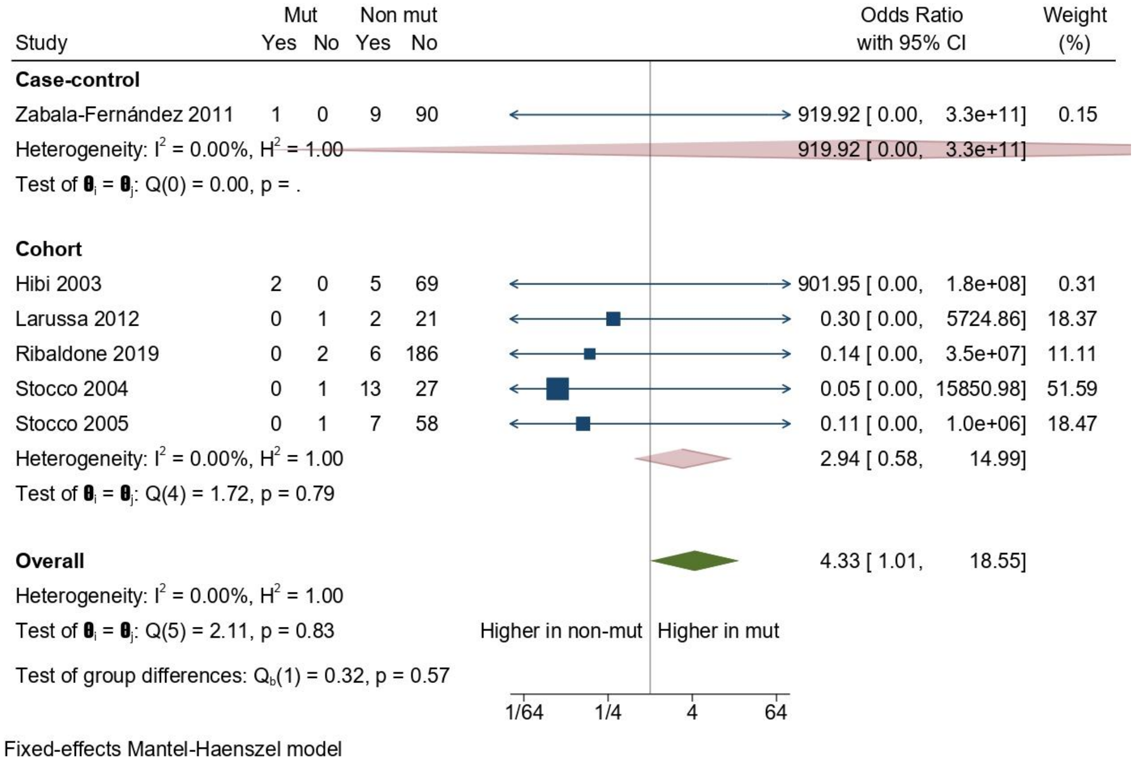


Figure S60. Forest plot of comparison mutated *TPMT2 vs wild-type, outcome: Total hematologic adverse events**

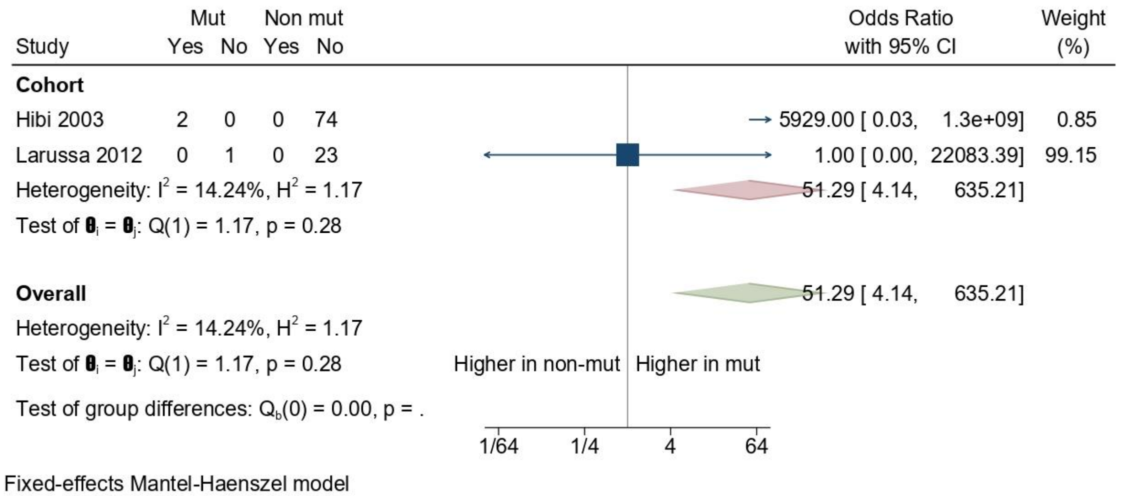


Figure S61. Forest plot of comparison mutated *TPMT2 vs wild-type, outcome: Serious hematologic adverse events**

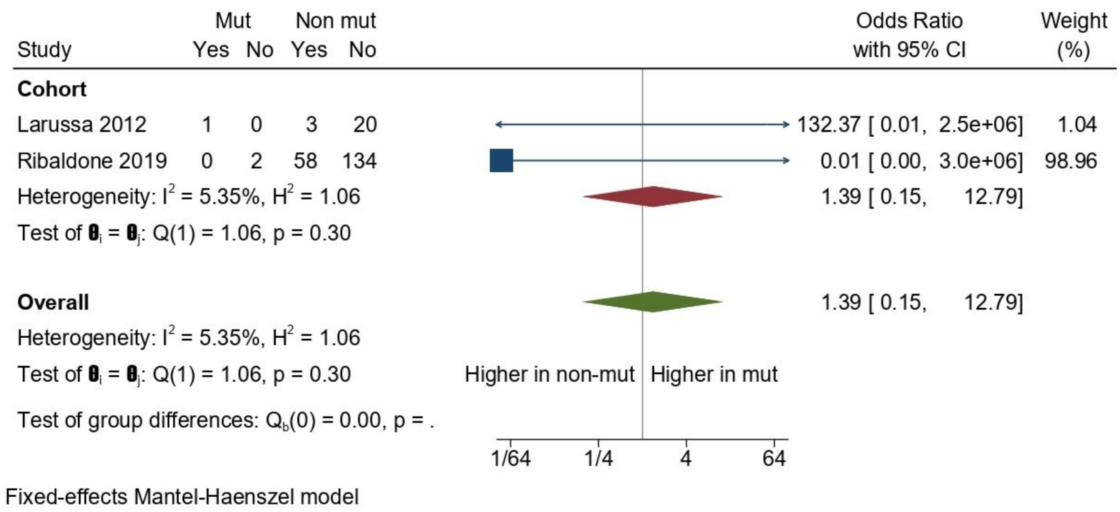


Figure S62. Forest plot of comparison mutated *TPMT2 vs wild-type, outcome: Withdrawal due to AE**

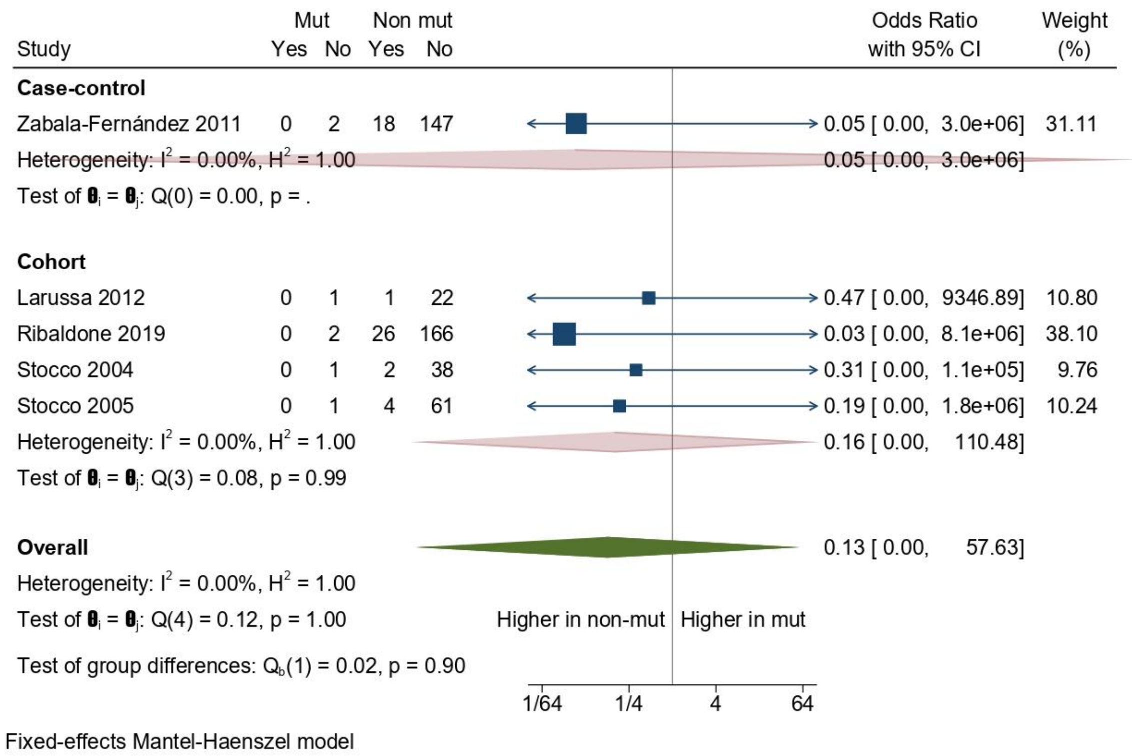


Figure S63. Forest plot of comparison mutated *TPMT2 vs wild-type, outcome: Pancreatitis**

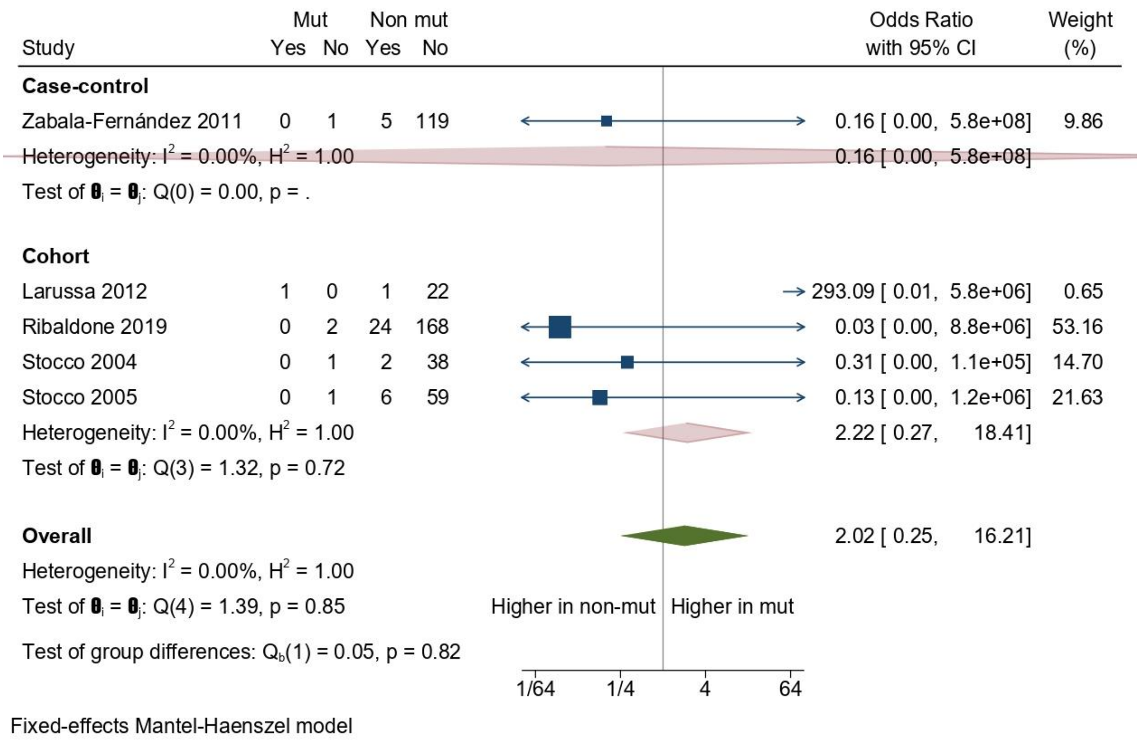


Figure S64. Forest plot of comparison mutated *TPMT2 vs wild-type, outcome: Hepatotoxicity**

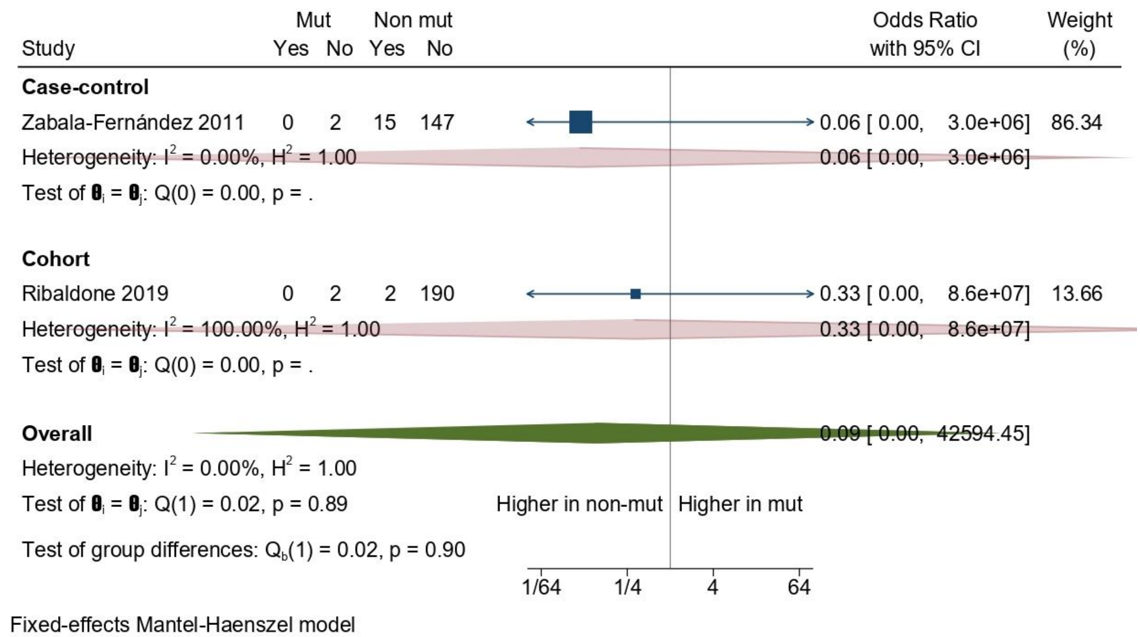


Figure S65. Forest plot of comparison mutated *TPMT2 vs wild-type, outcome: Gastrointestinal side effects**

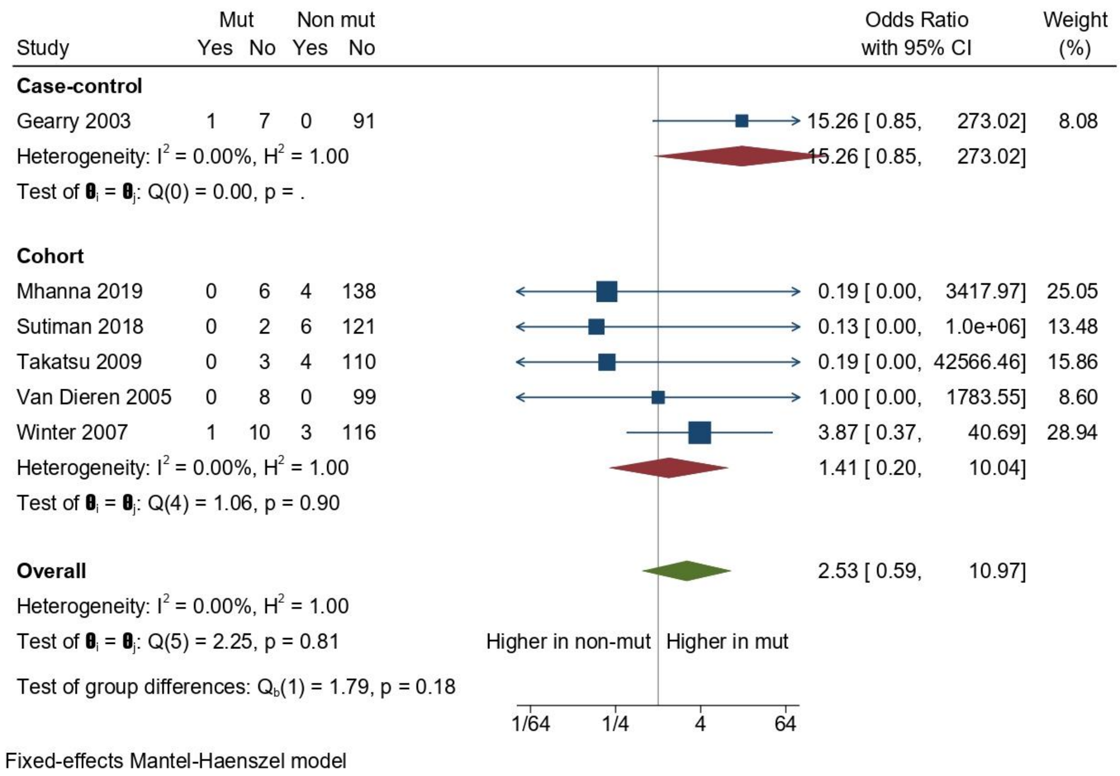


Figure S66. Forest plot of comparison *TPMT3 heterozygous vs wild-type, outcome: Total serious adverse events**

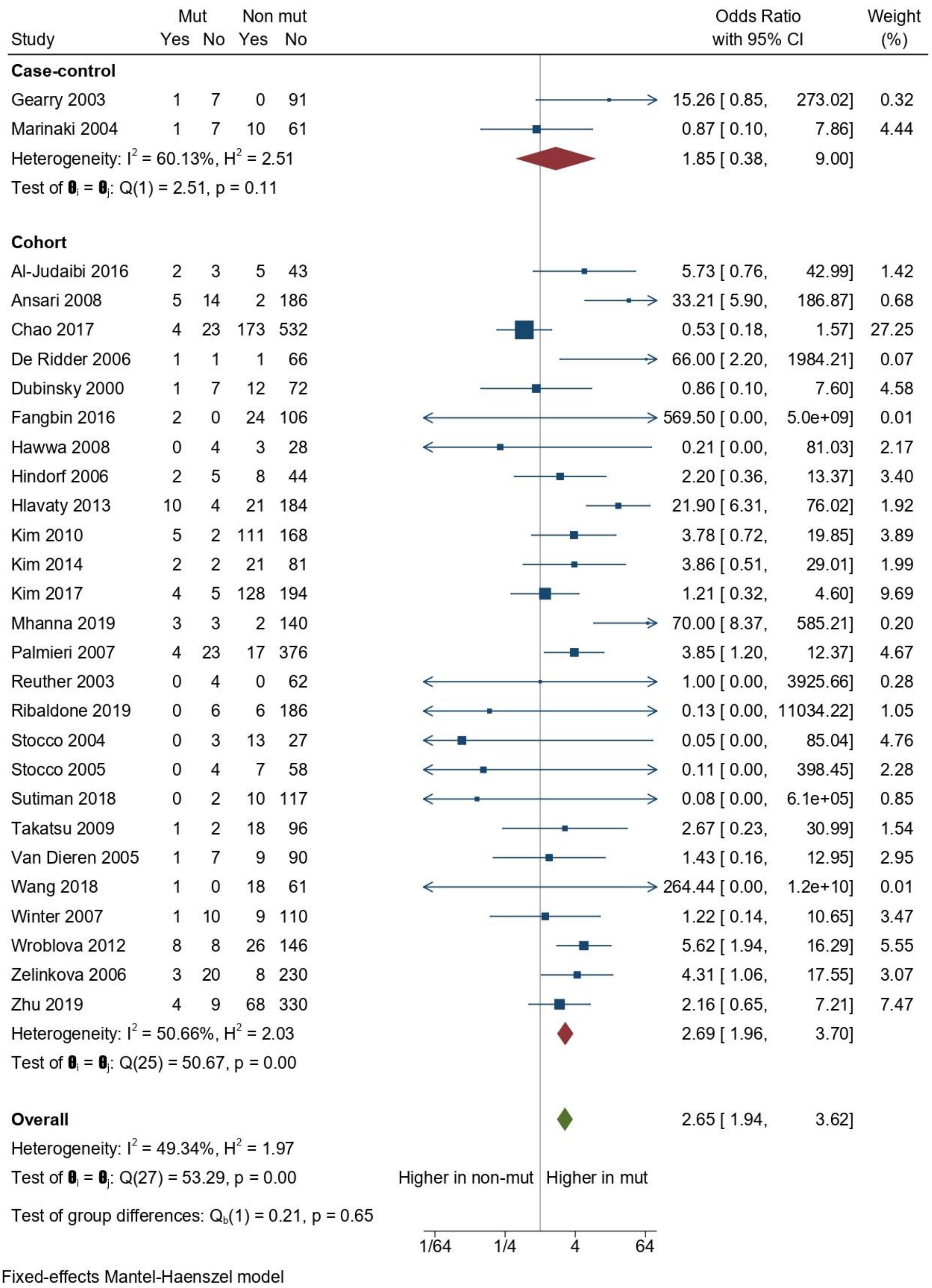


Figure S67. Forest plot of comparison *TPMT3 heterozygous vs wild-type, outcome: Total hematologic adverse events**

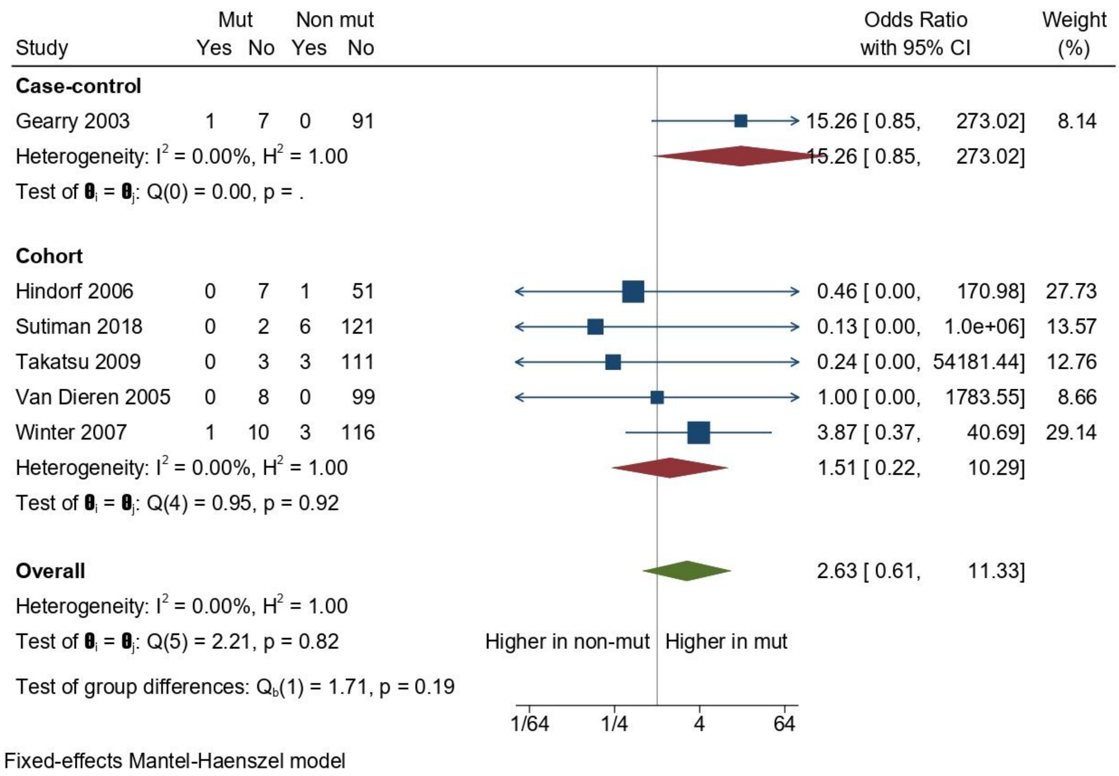


Figure S68. Forest plot of comparison *TPMT3 heterozygous vs wild-type, outcome: Serious hematologic adverse events**

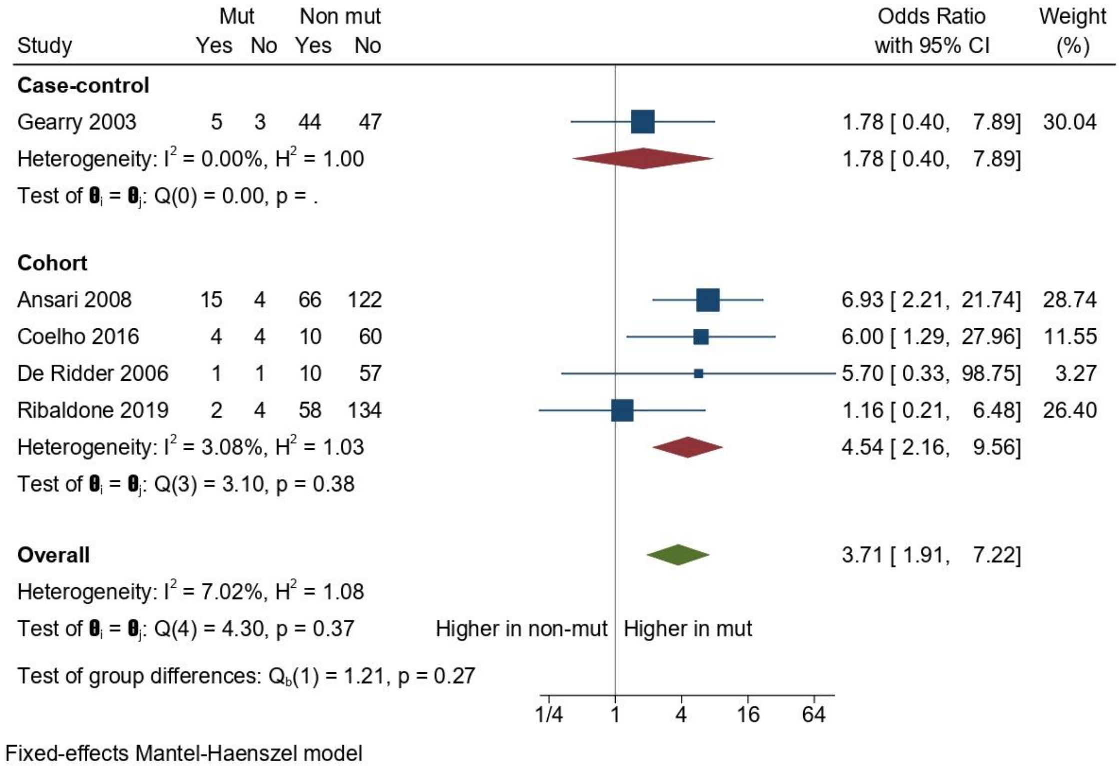


Figure S69. Forest plot of comparison *TPMT3 heterozygous vs wild-type, outcome: Withdrawal due to AE**

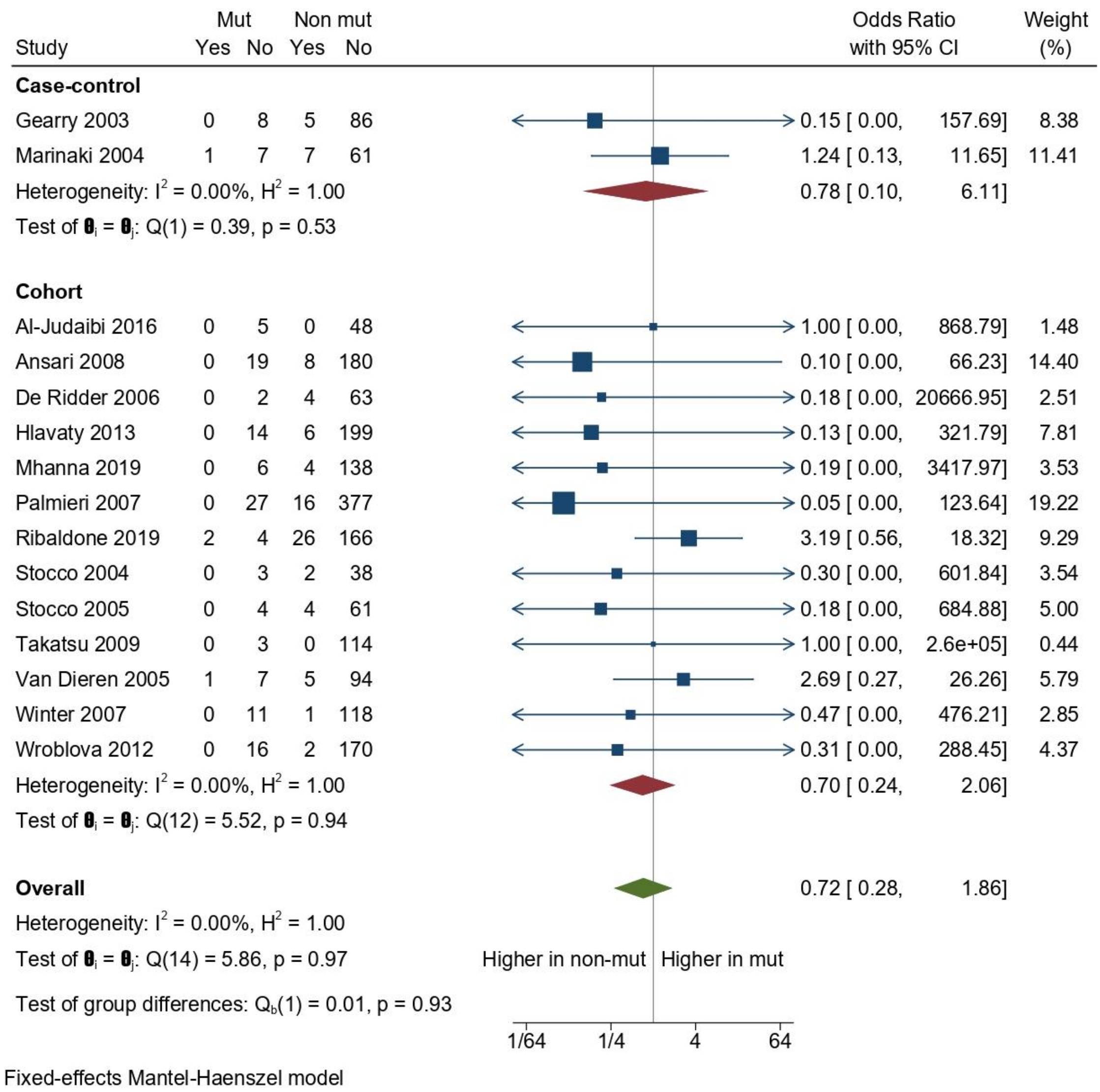


Figure S70. Forest plot of comparison *TPMT3 heterozygous vs wild-type, outcome: Pancreatitis**

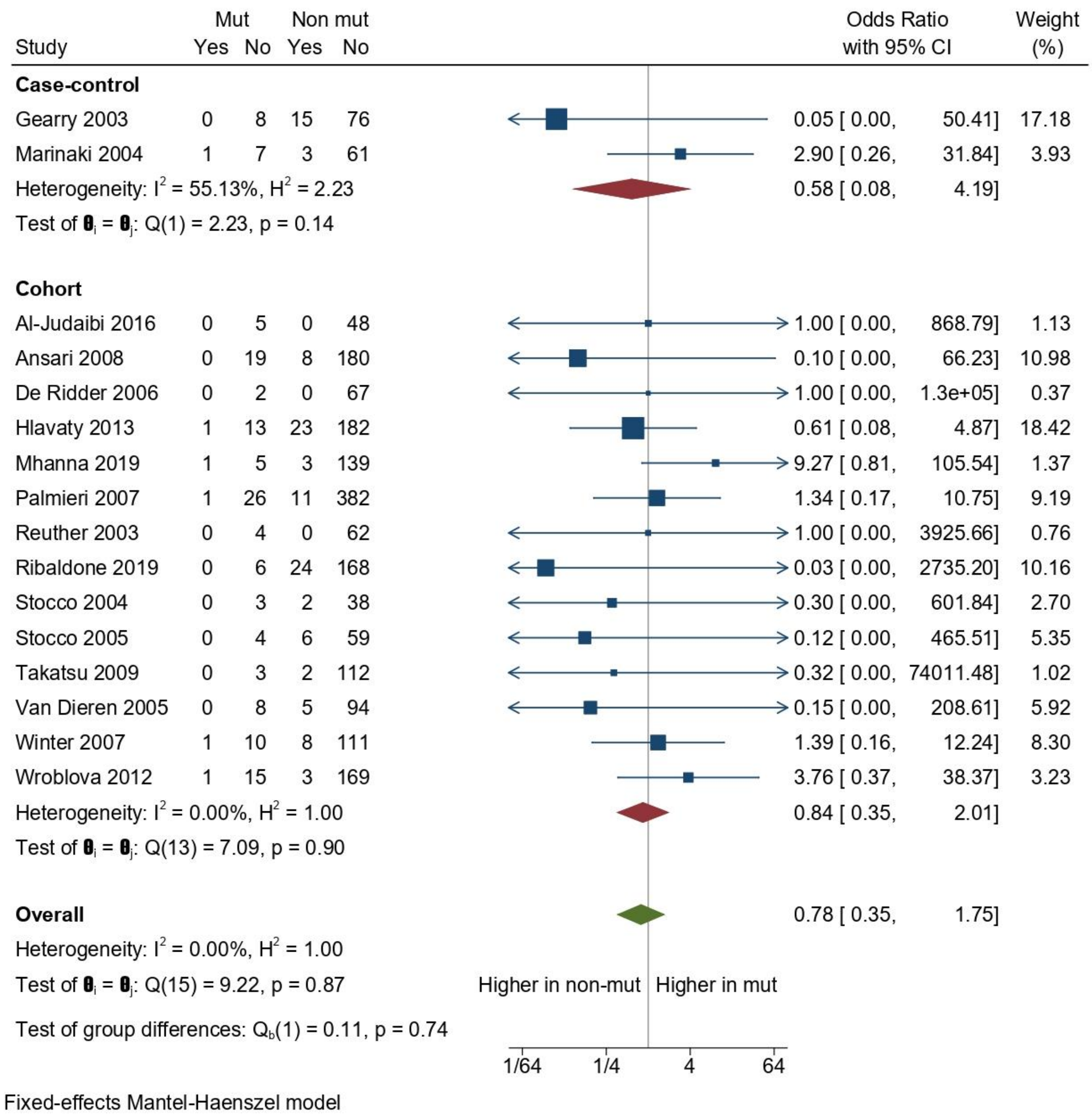


Figure S71. Forest plot of comparison *TPMT3 heterozygous vs wild-type, outcome: Hepatotoxicity**

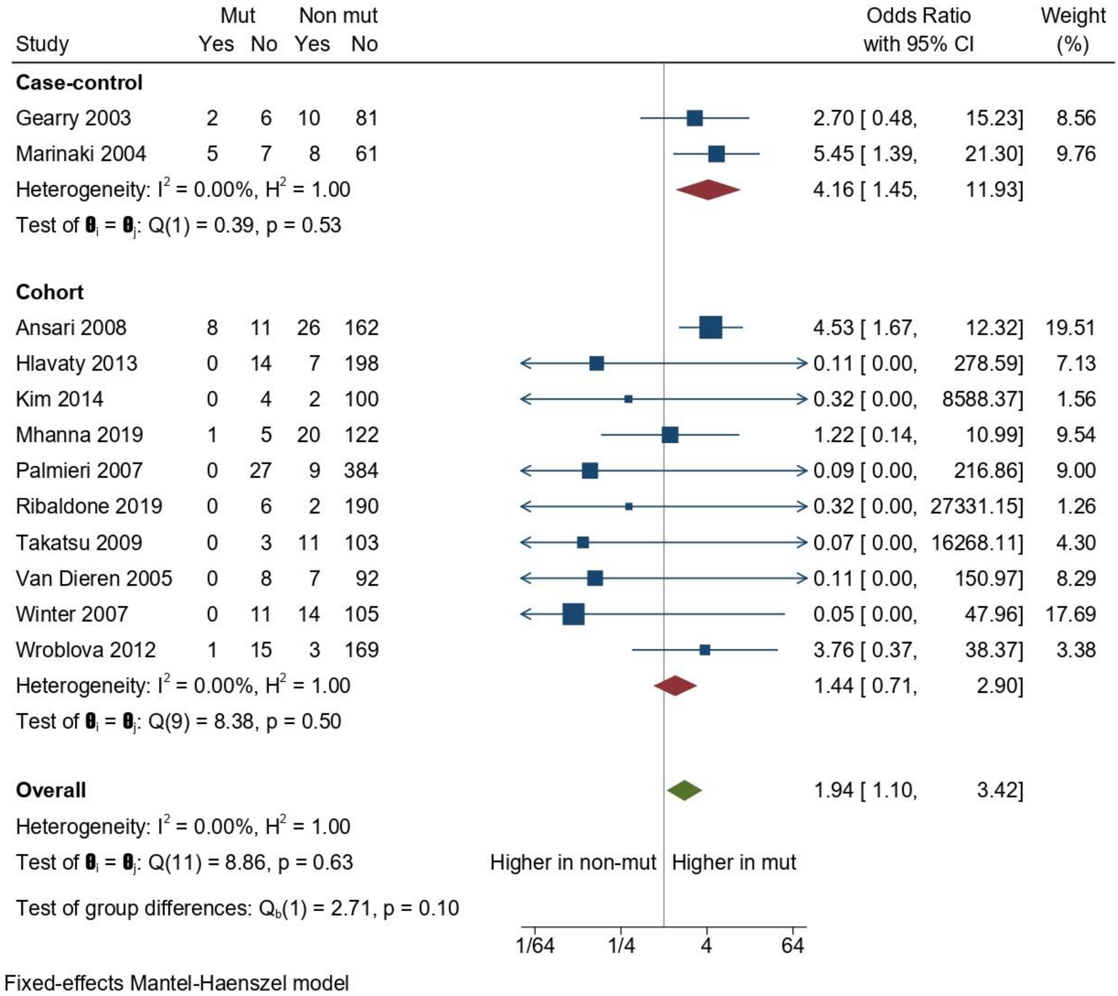


Figure S72. Forest plot of comparison *TPMT3 heterozygous vs wild-type, outcome: Gastrointestinal side effects**

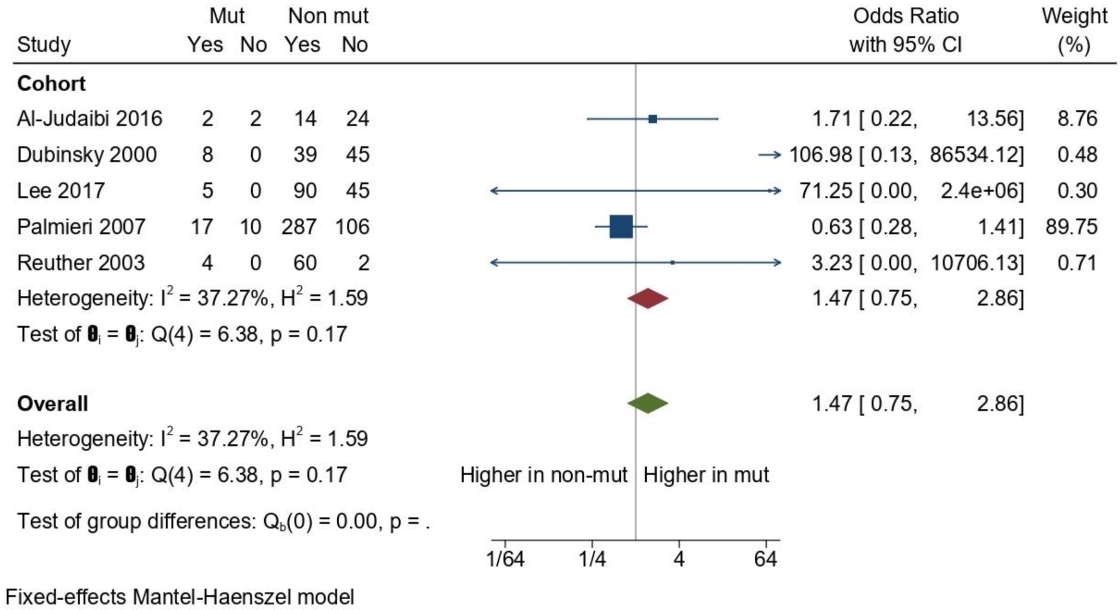


Figure S73. Forest plot of comparison *TPMT3 heterozygous vs wild-type, outcome: Clinical remission**

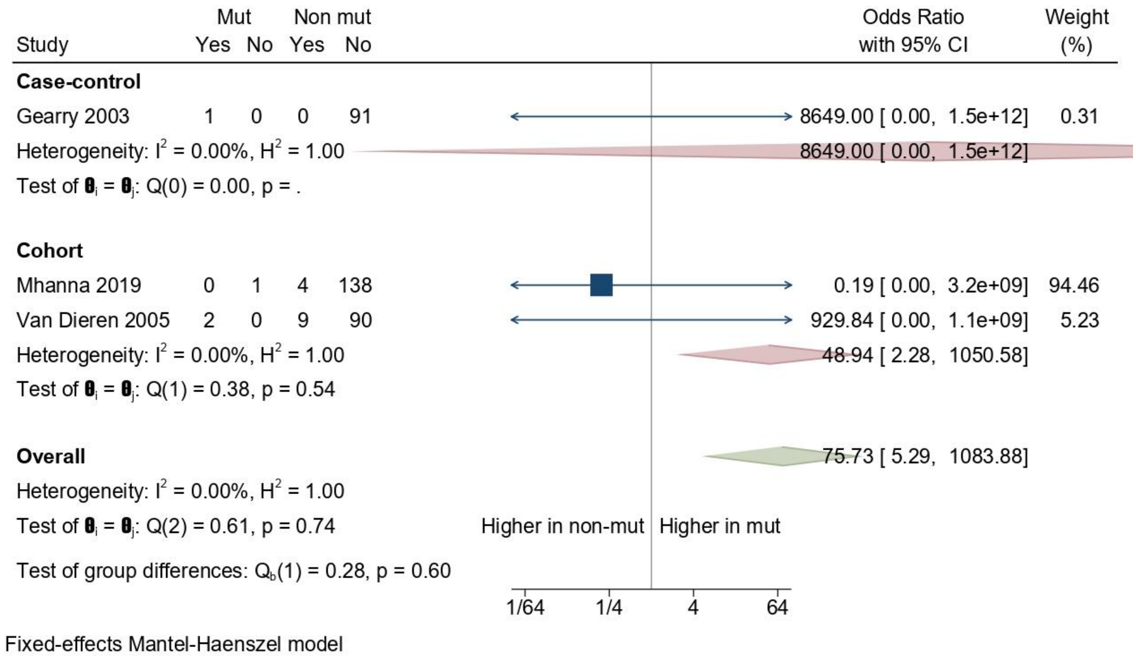


Figure S74. Forest plot of comparison *TPMT3, 2 mutant alleles vs wild-type, outcome: Total serious adverse events**

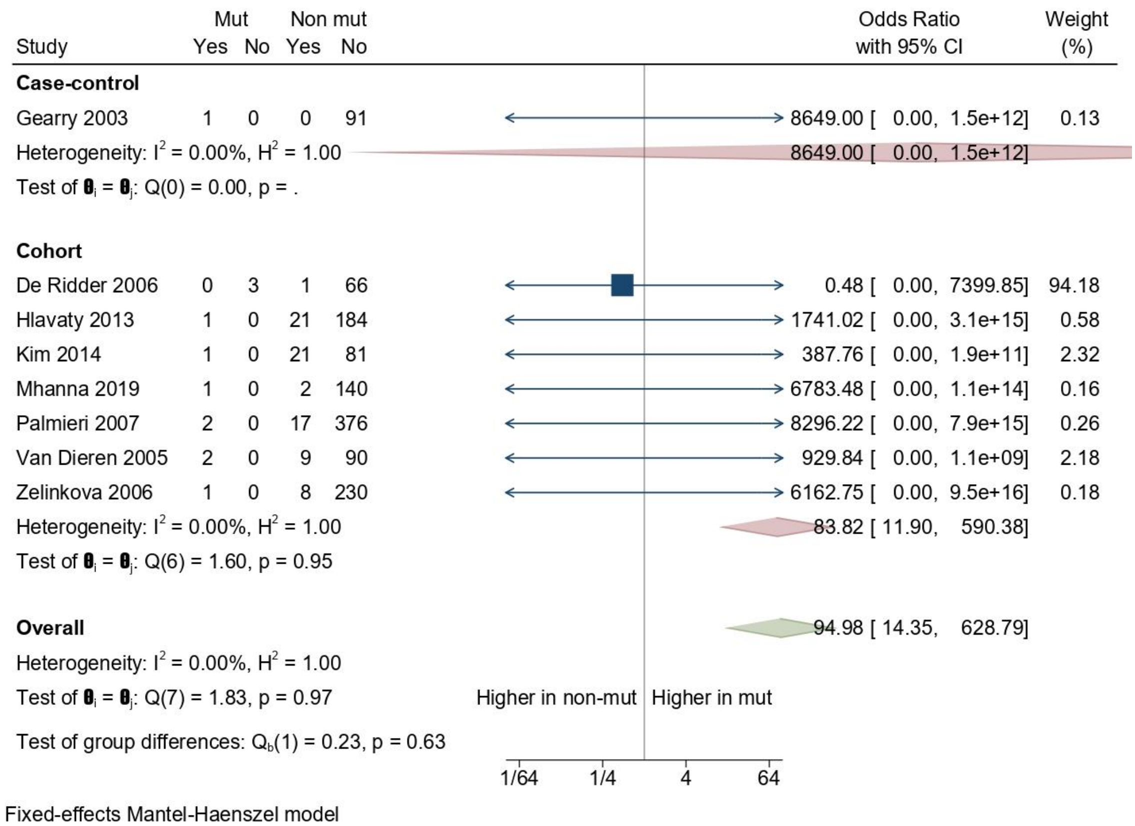


Figure S75. Forest plot of comparison *TPMT3, 2 mutant alleles vs wild-type, outcome: Total hematologic adverse events**

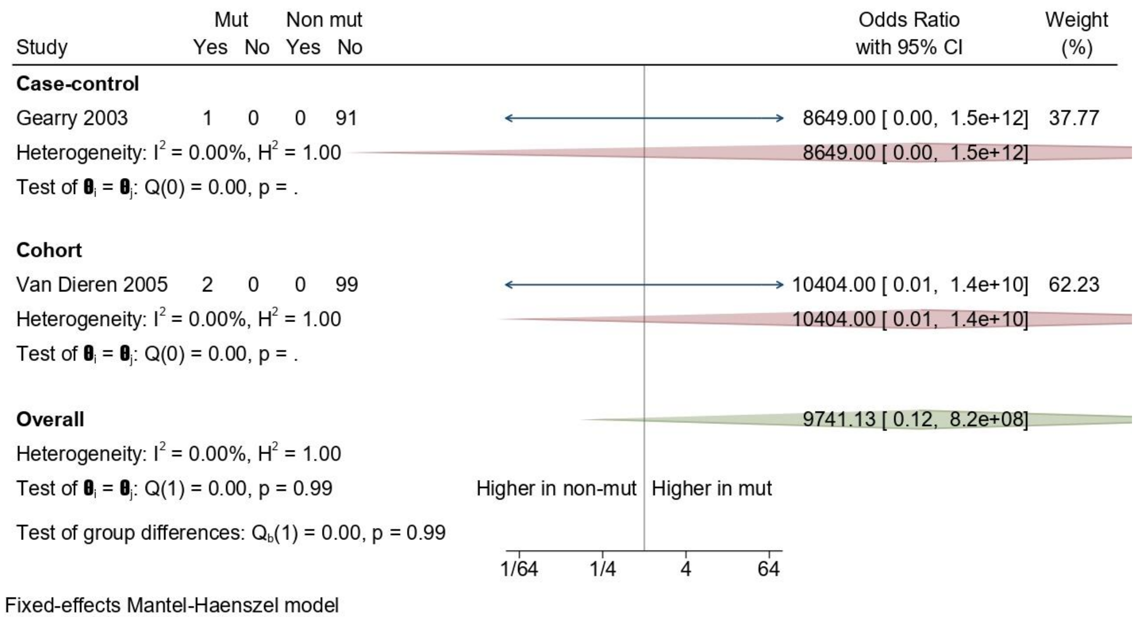


Figure S76. Forest plot of comparison *TPMT3, 2 mutant alleles vs wild-type, outcome: Serious hematologic adverse events**

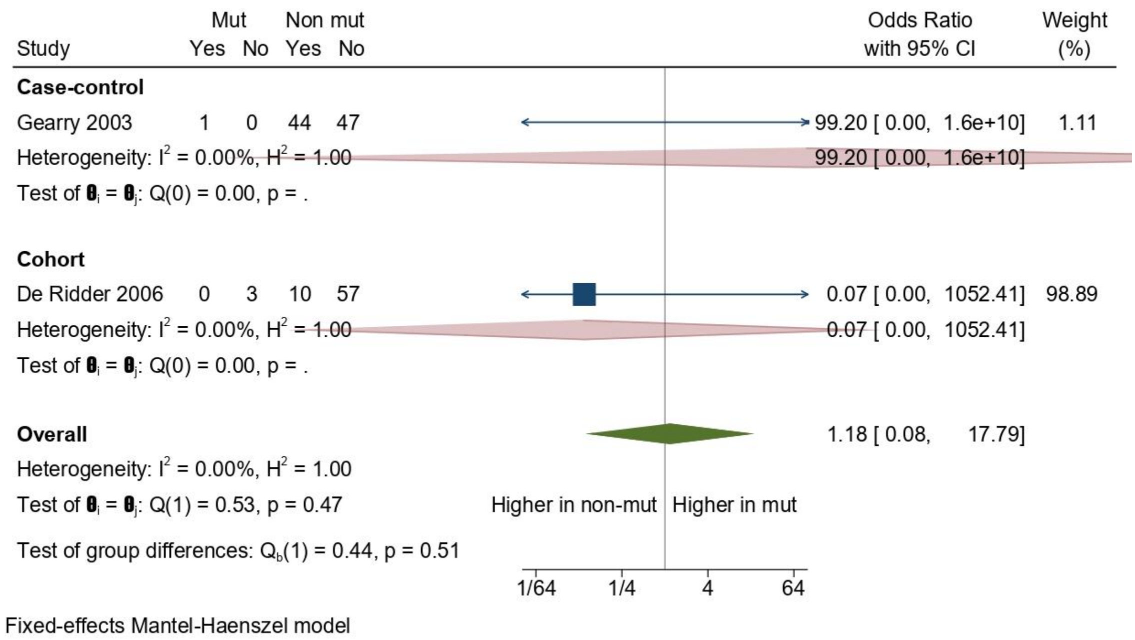


Figure S77. Forest plot of comparison *TPMT3, 2 mutant alleles vs wild-type, outcome: Withdrawal due to AE**

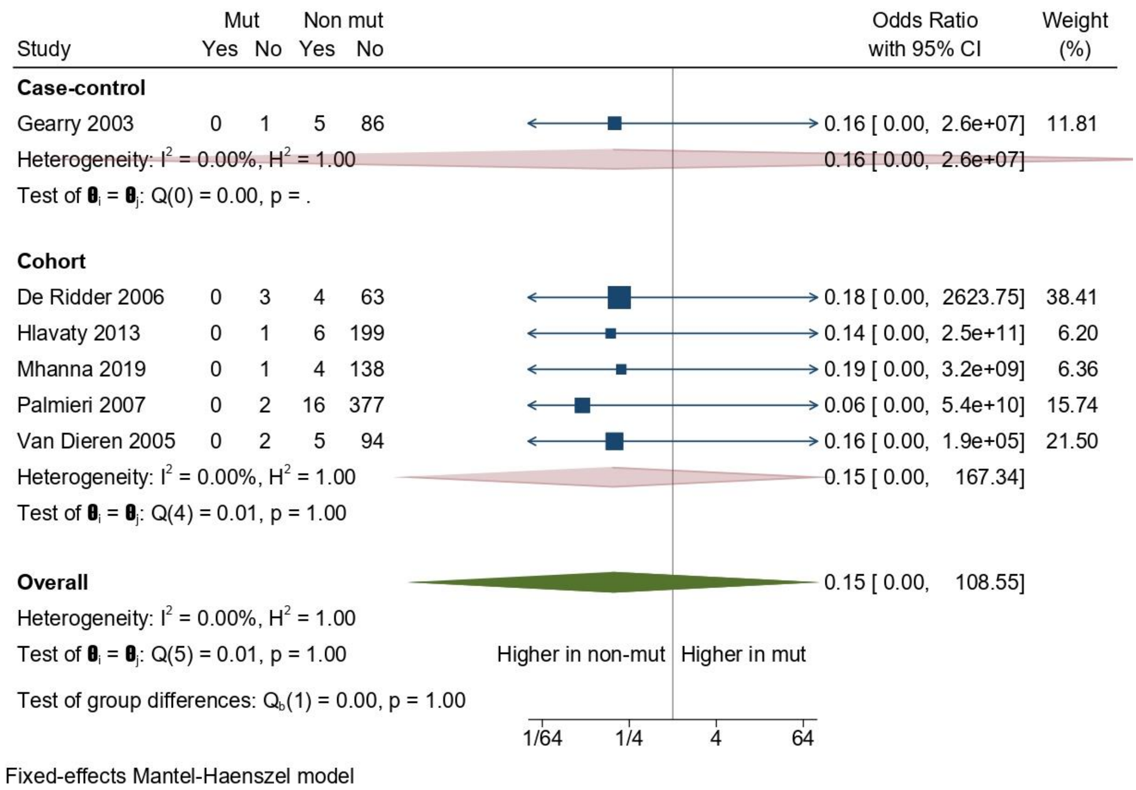


Figure S78. Forest plot of comparison *TPMT3, 2 mutant alleles vs wild-type, outcome: Pancreatitis**

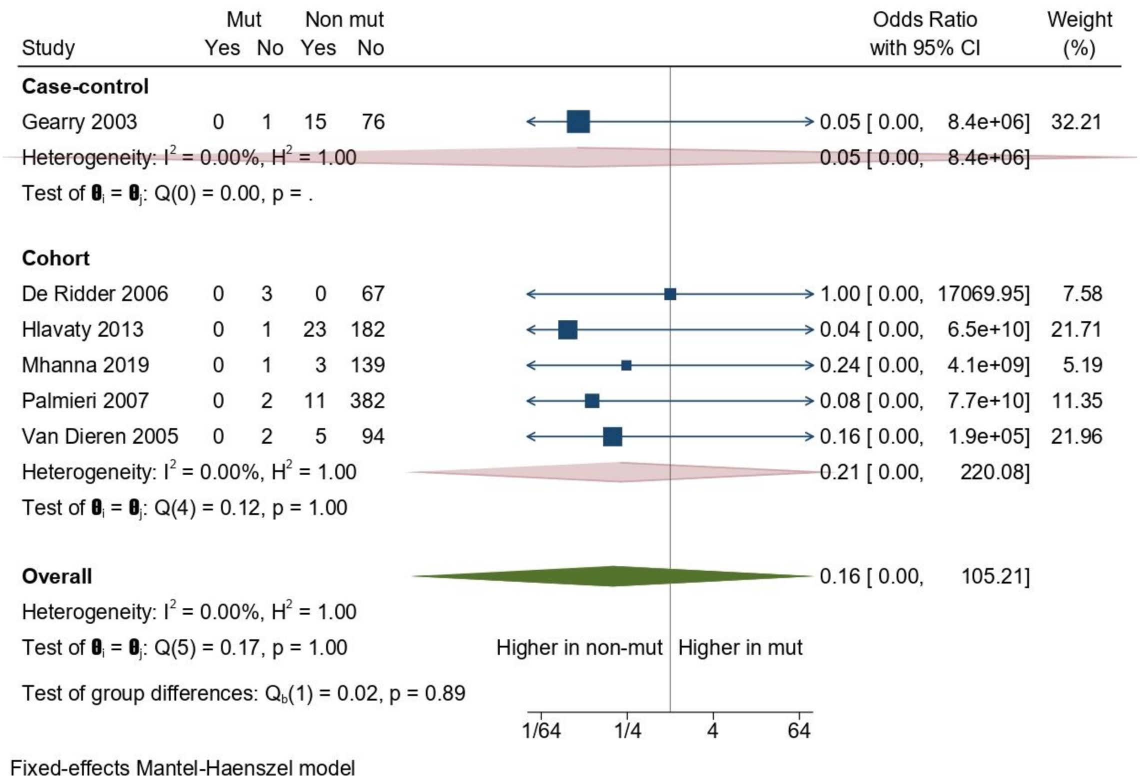


Figure S79. Forest plot of comparison *TPMT3, 2 mutant alleles vs wild-type, outcome: Hepatotoxicity**

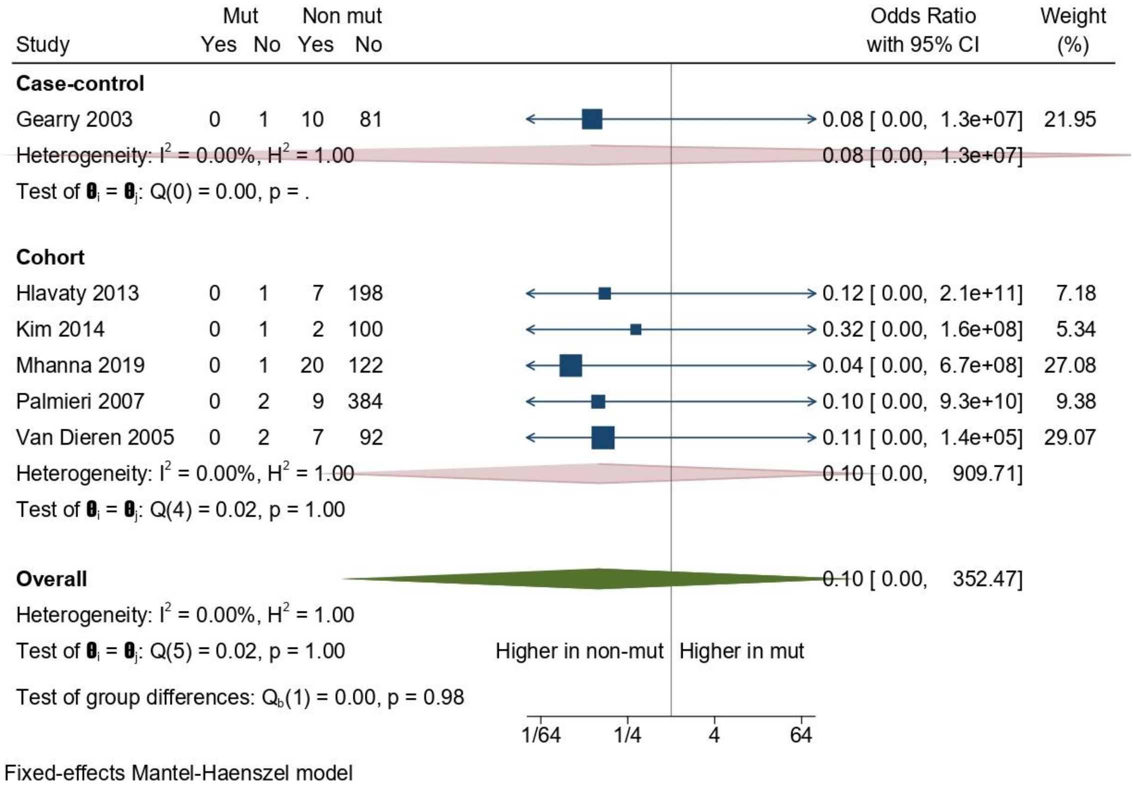


Figure S80. Forest plot of comparison *TPMT3, 2 mutant alleles vs wild-type, outcome: Gastrointestinal side effects**

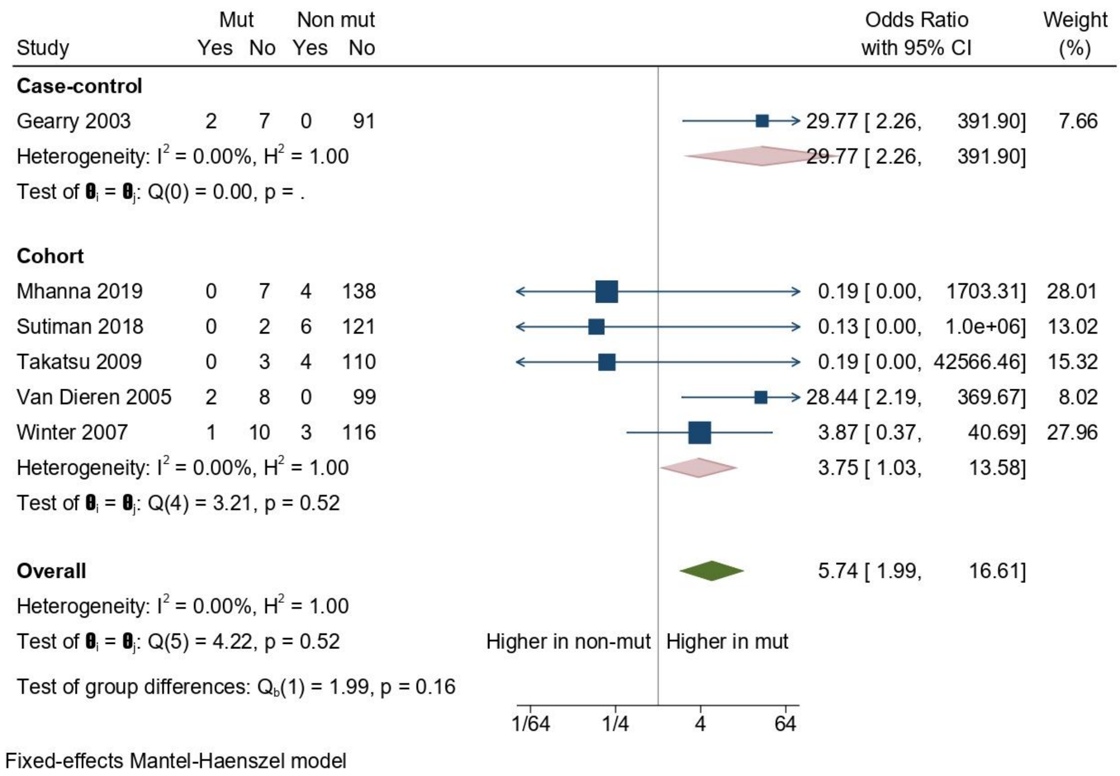


Figure S81. Forest plot of comparison *TPMT3 vs wild-type, outcome: Total serious adverse events**

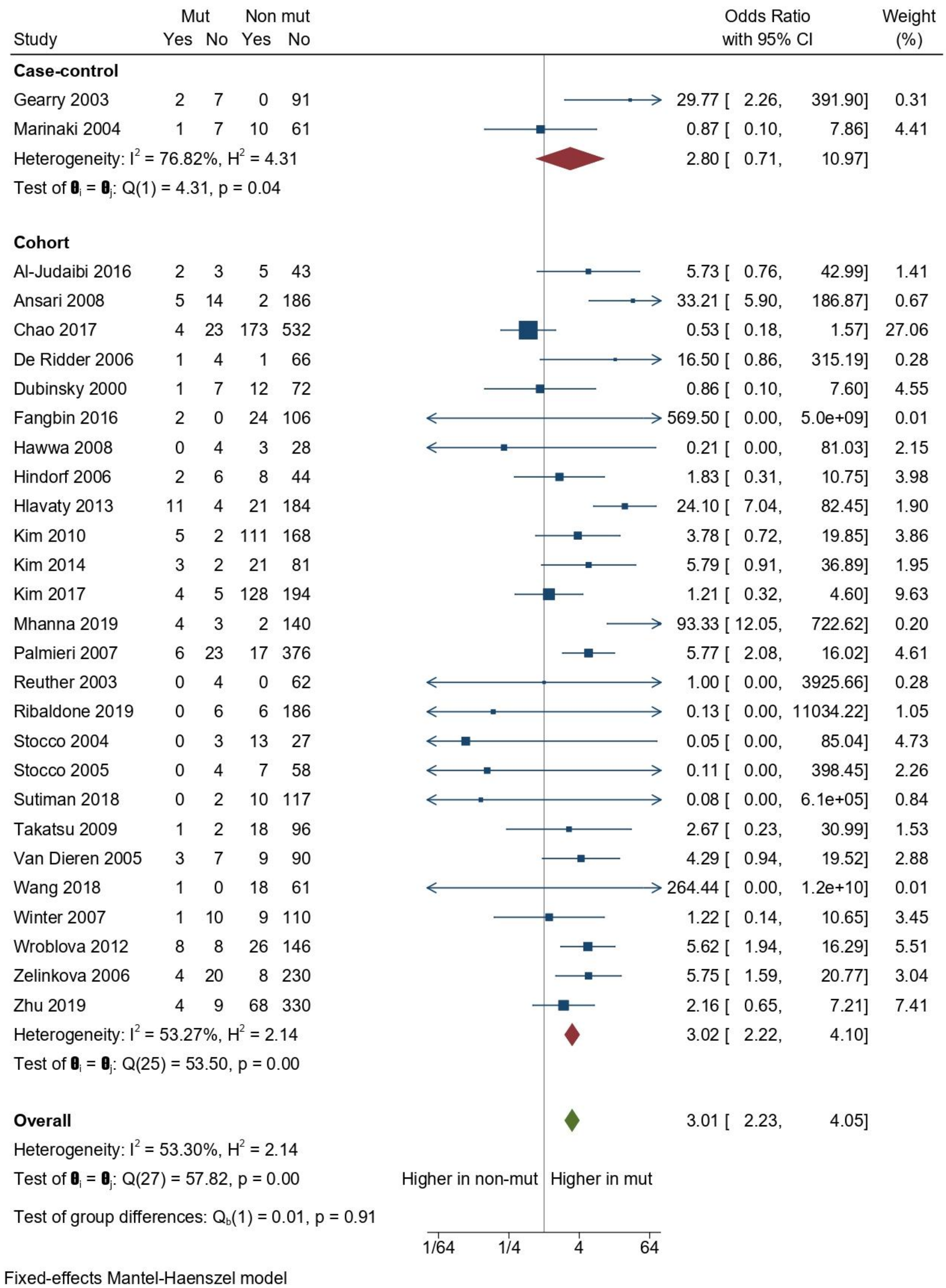


Figure S82. Forest plot of comparison *TPMT3 vs wild-type, outcome: Total hematologic adverse events**

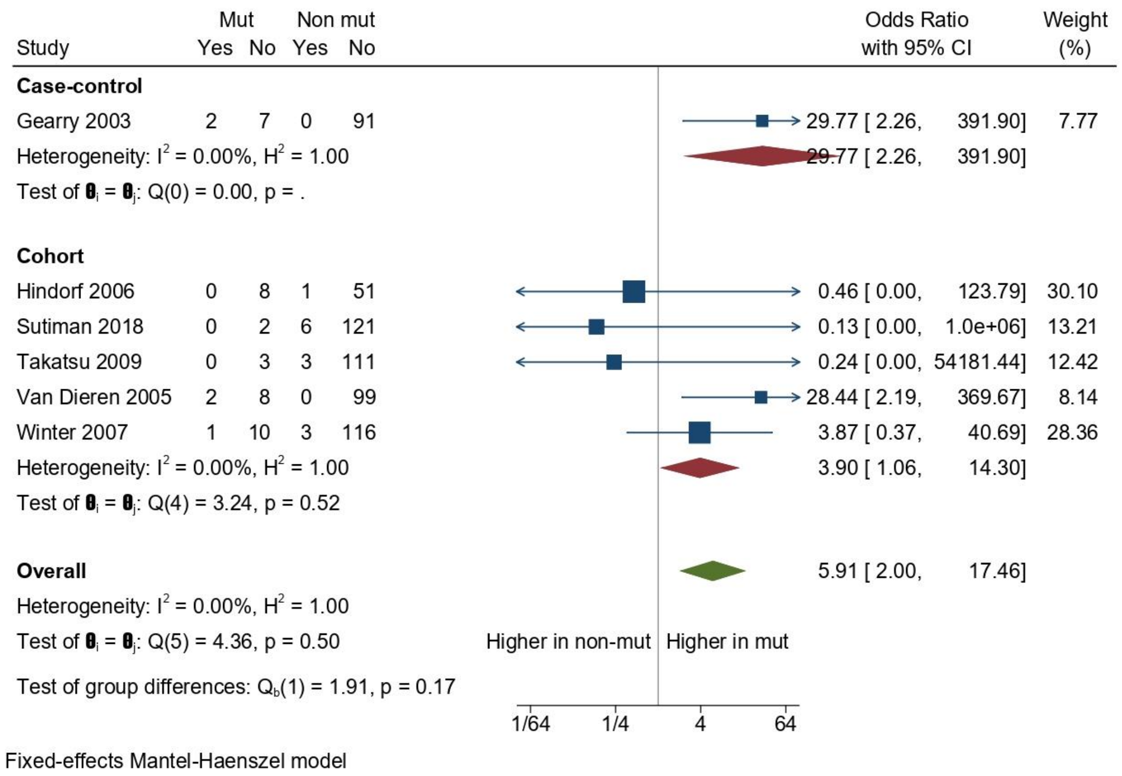


Figure S83. Forest plot of comparison *TPMT3 vs wild-type, outcome: Serious hematologic adverse events**

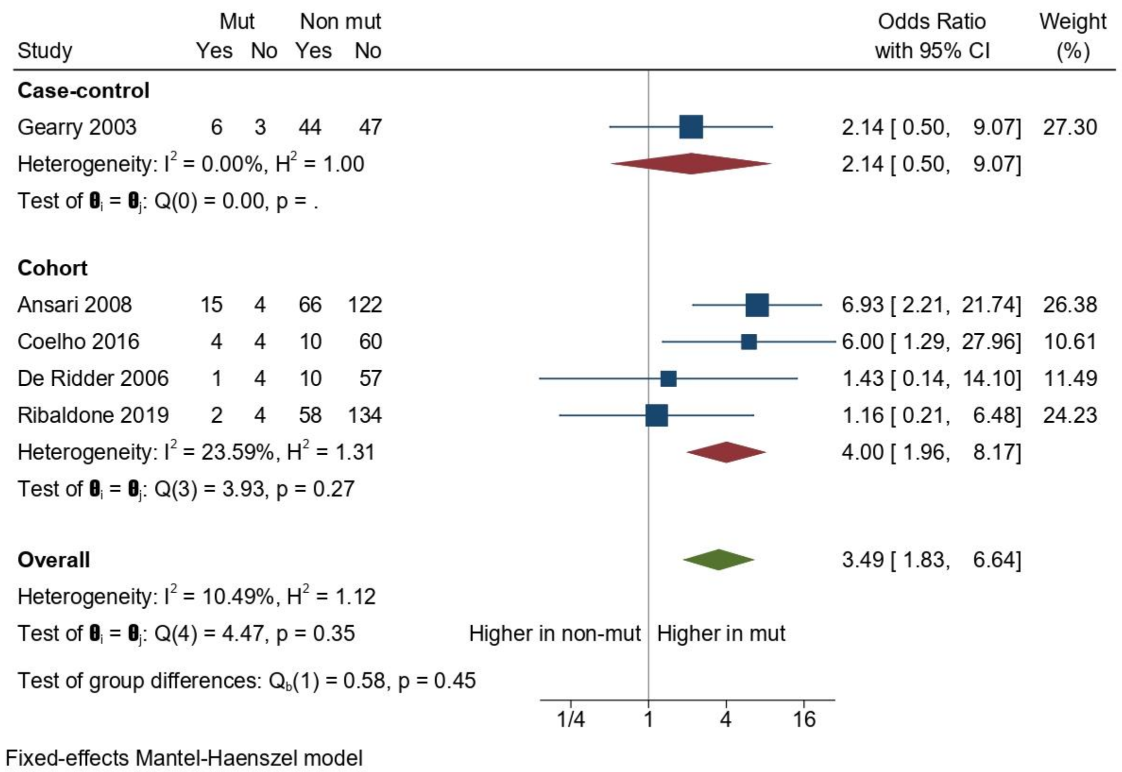


Figure S84. Forest plot of comparison *TPMT3 vs wild-type, outcome: Withdrawal due to AE**

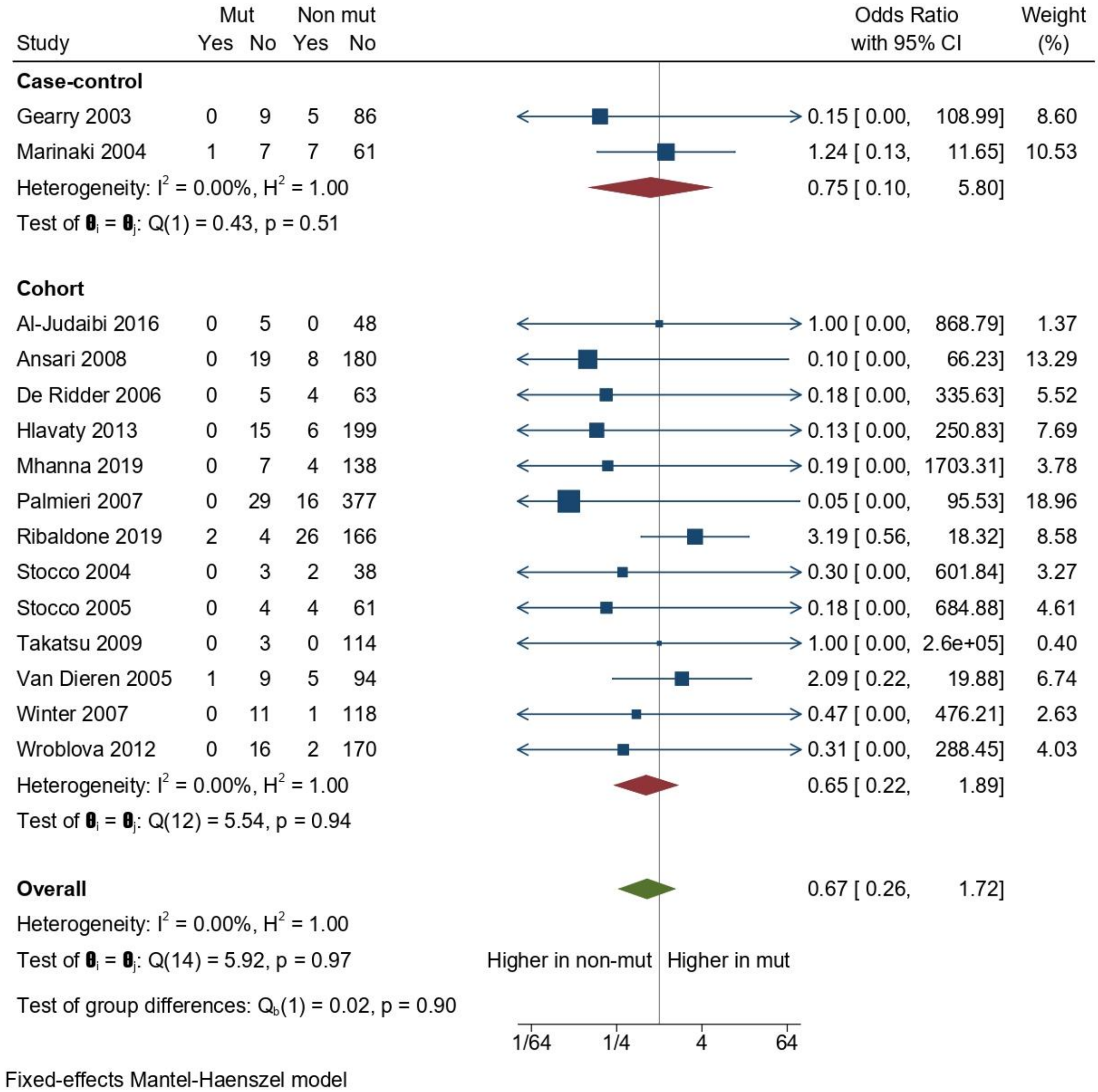


Figure S85. Forest plot of comparison *TPMT3 vs wild-type, outcome: Pancreatitis**

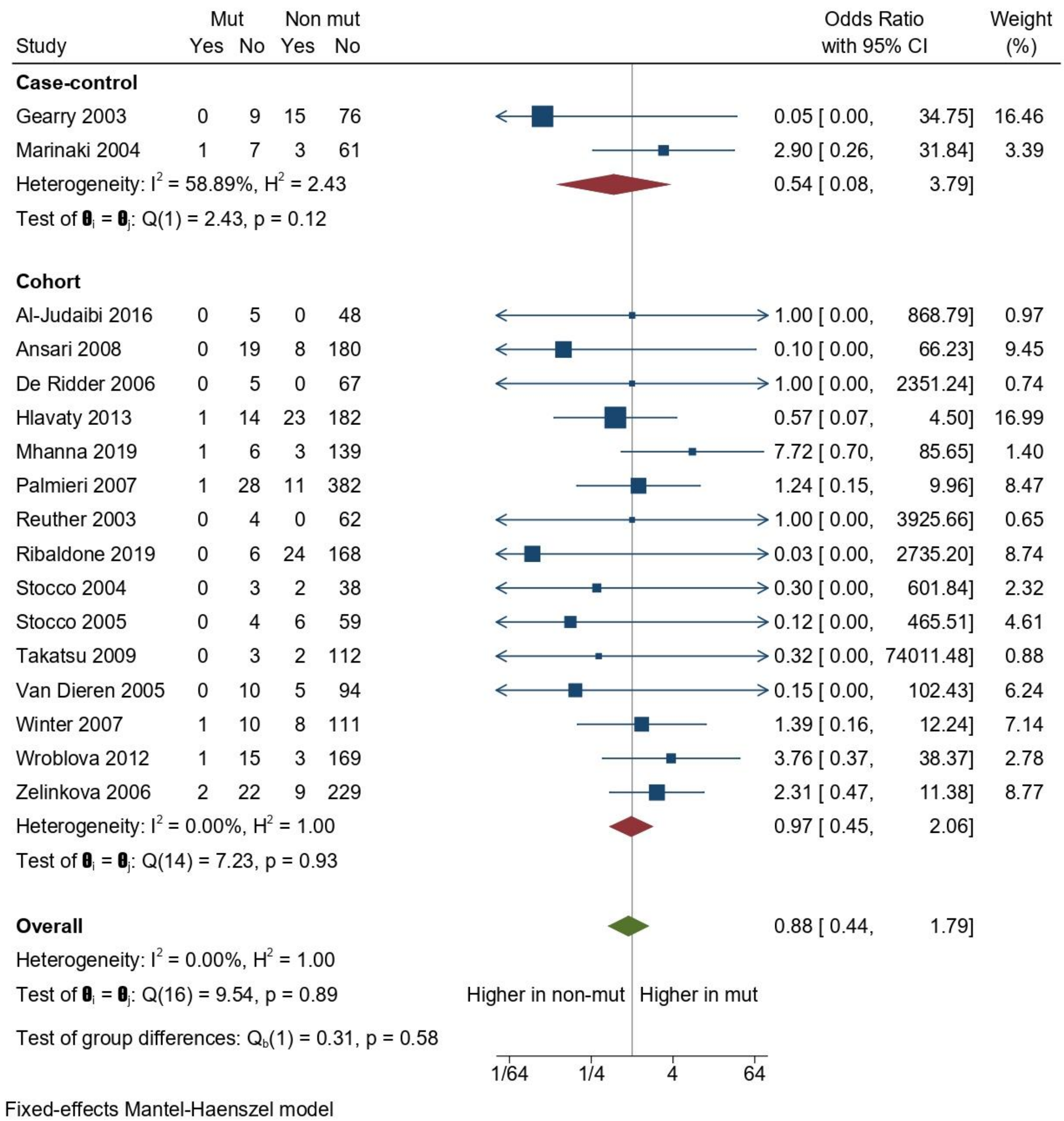


Figure S86. Forest plot of comparison *TPMT3 vs wild-type, outcome: Hepatotoxicity**

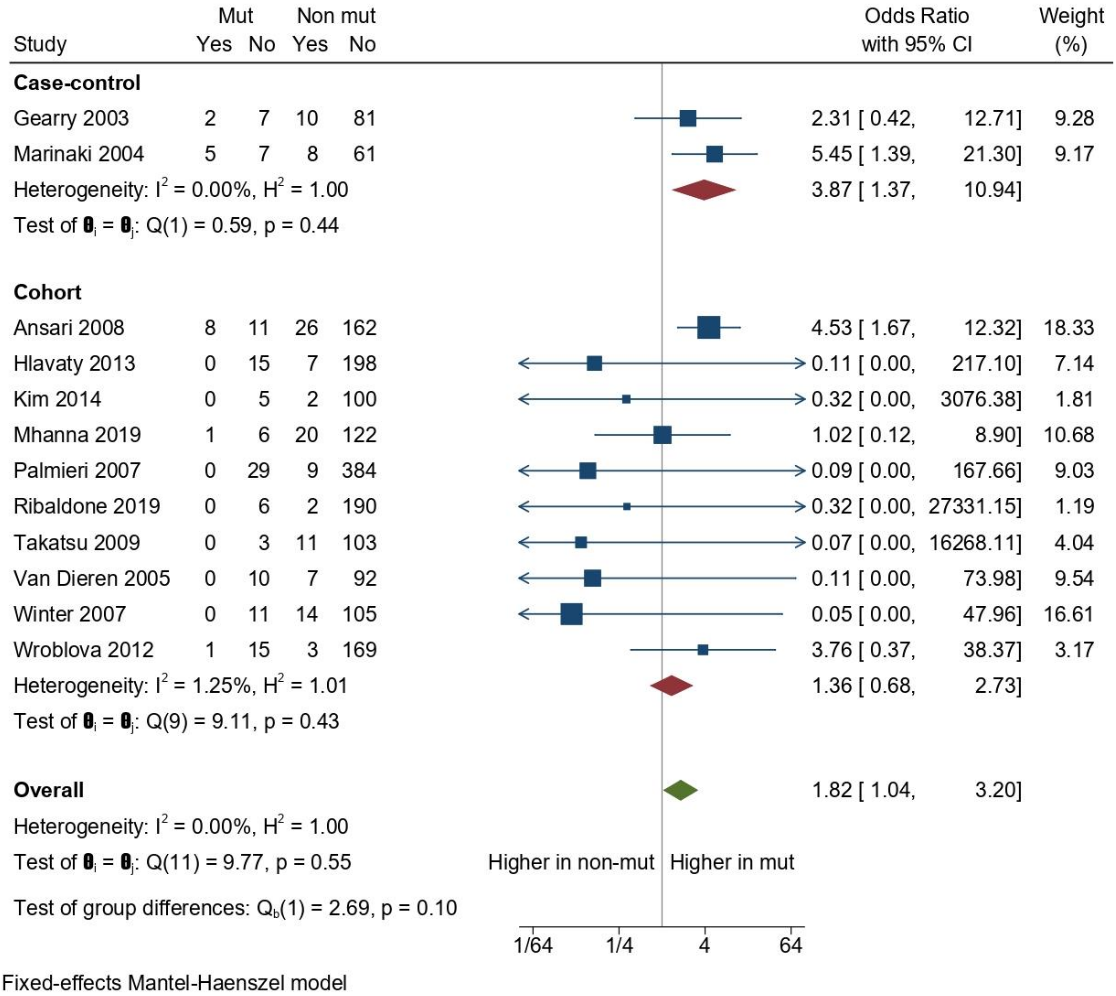


Figure S87. Forest plot of comparison *TPMT3 vs wild-type, outcome: Gastrointestinal side effects**

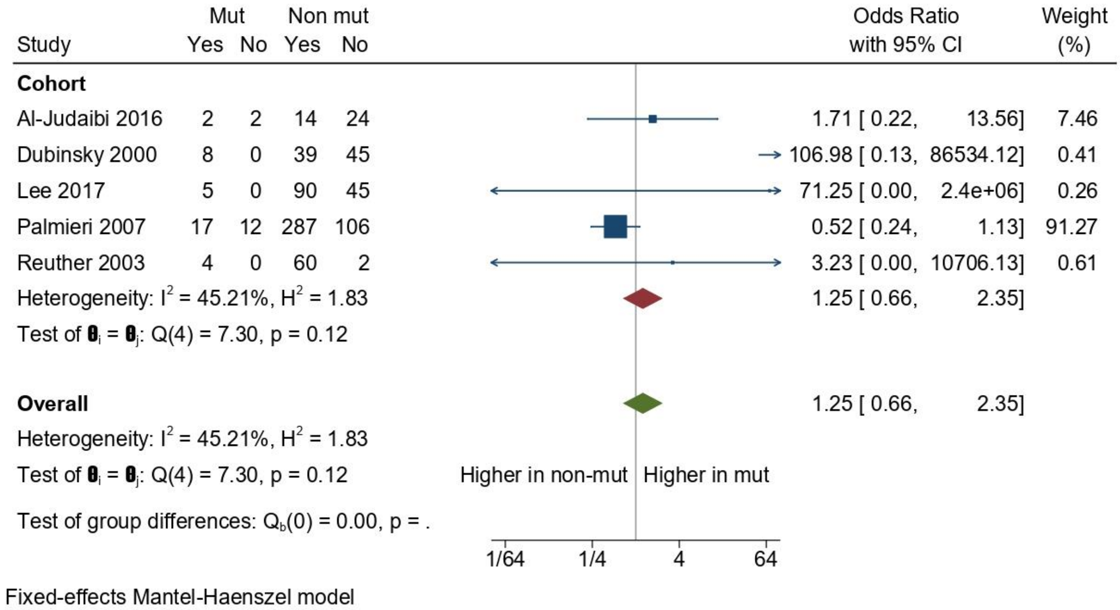


Figure S88. Forest plot of comparison *TPMT3 vs wild-type, outcome: Clinical remission**

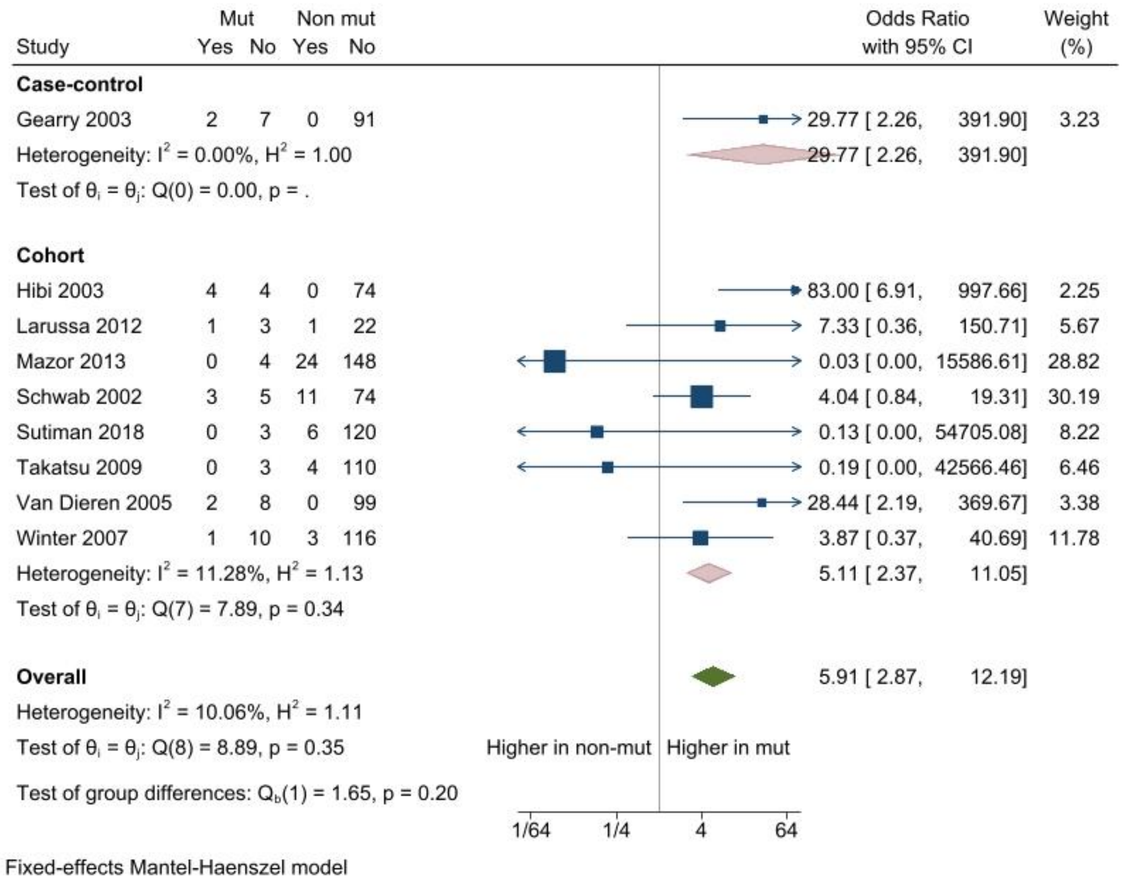
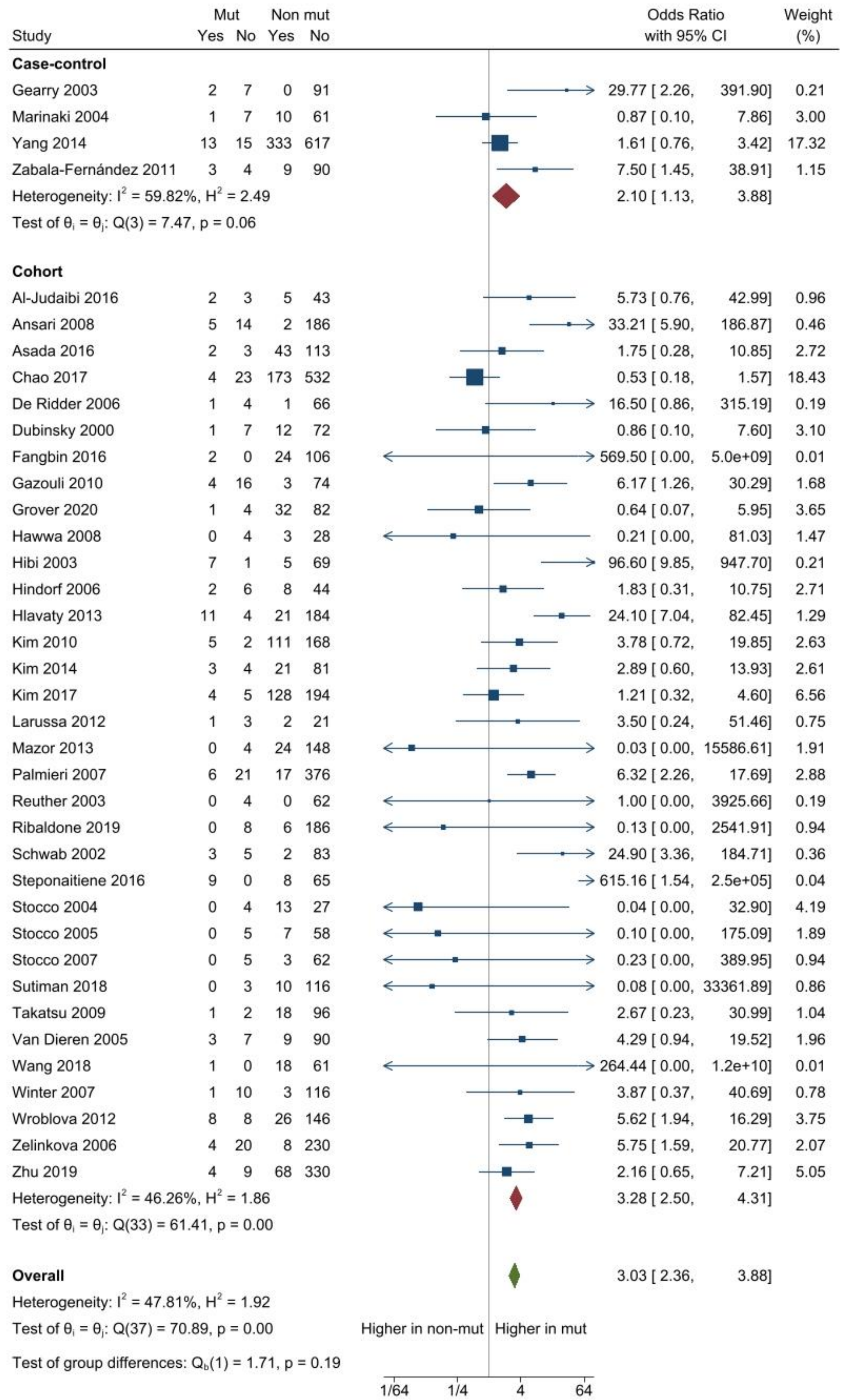


Figure S89. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *TPMT* vs wild-type, outcome: Total SAE



Fixed-effects Mantel-Haenszel model

Figure S90. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *TPMT* vs wild-type, outcome: Total hematologic AE

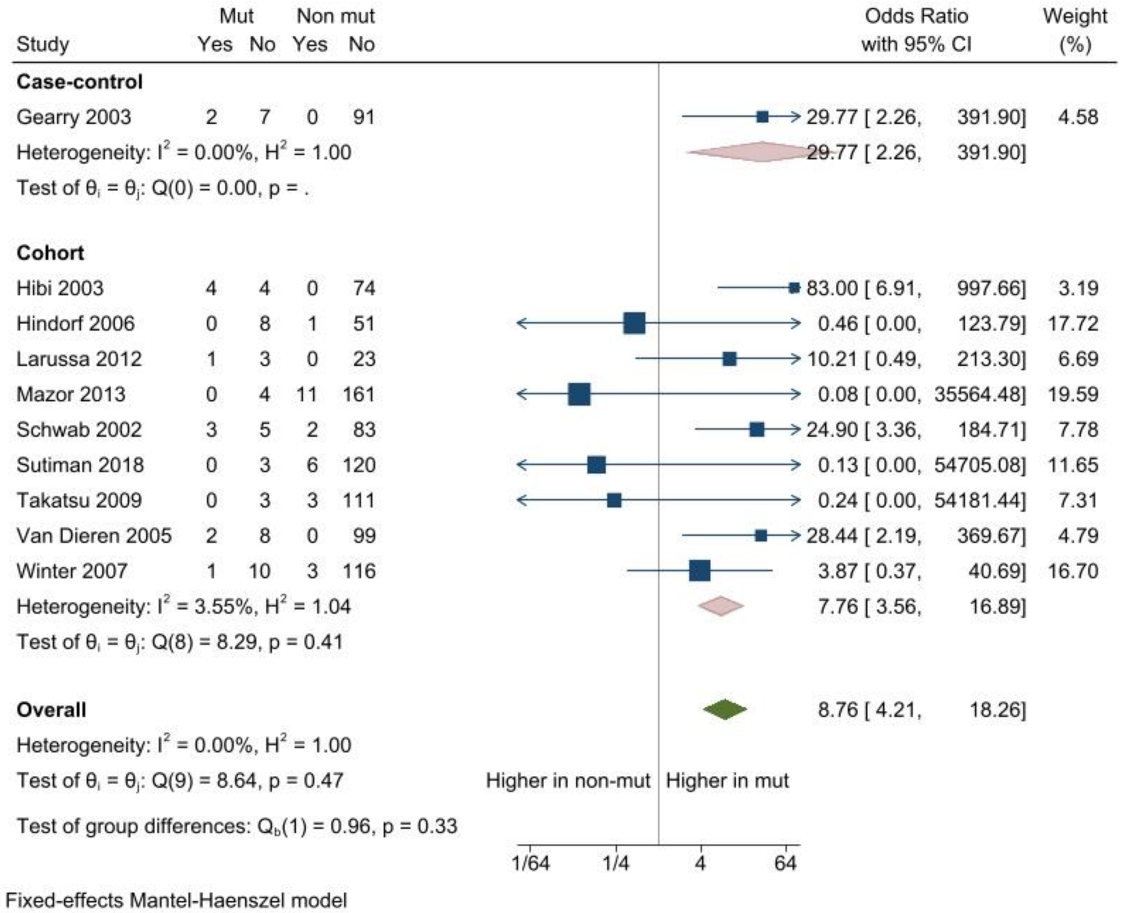


Figure S91. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *TPMT* vs wild-type, outcome: Serious hematologic AE

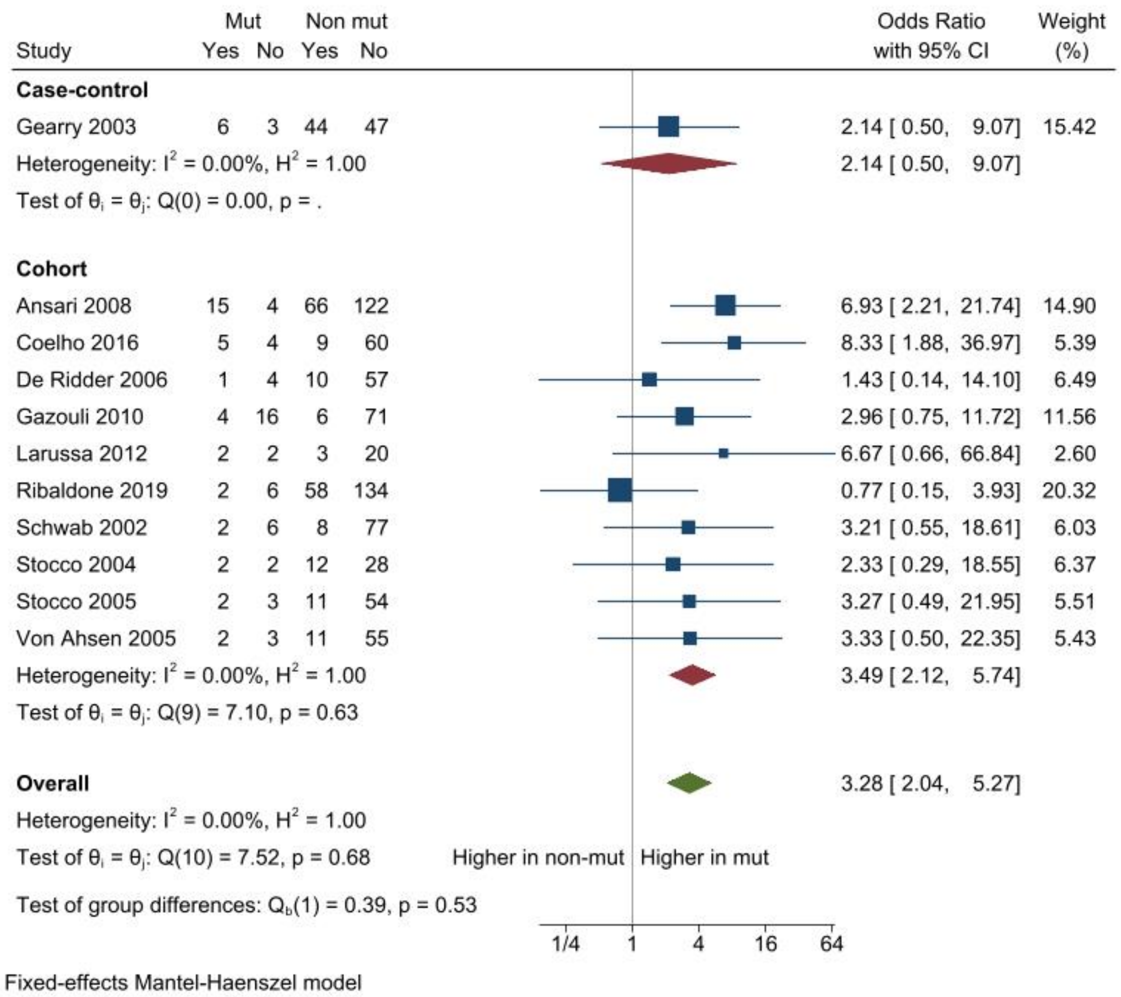


Figure S92. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *TPMT* vs wild-type, outcome: Withdrawal due to AE

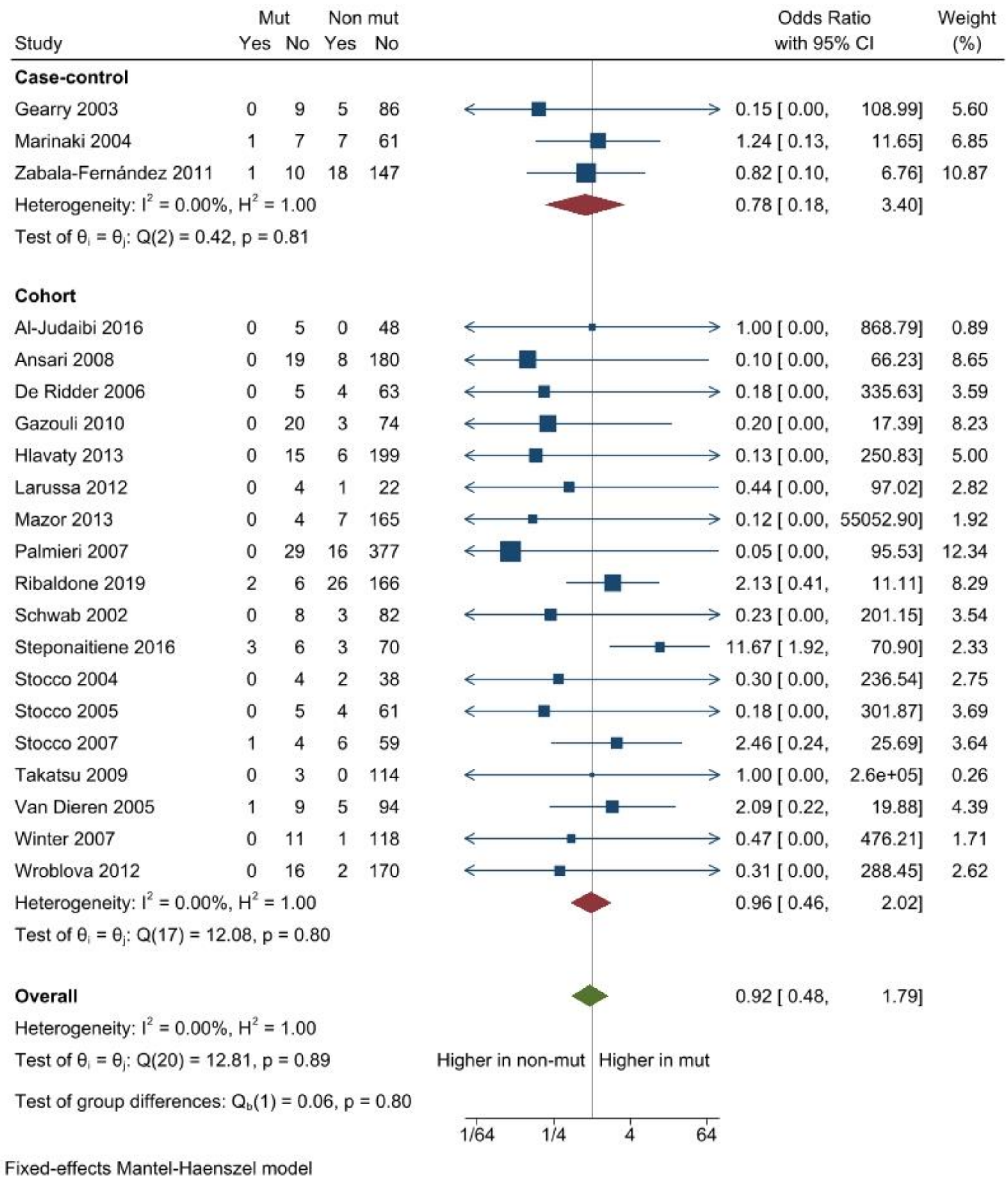


Figure S93. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *TPMT* vs wild-type, outcome: Pancreatitis

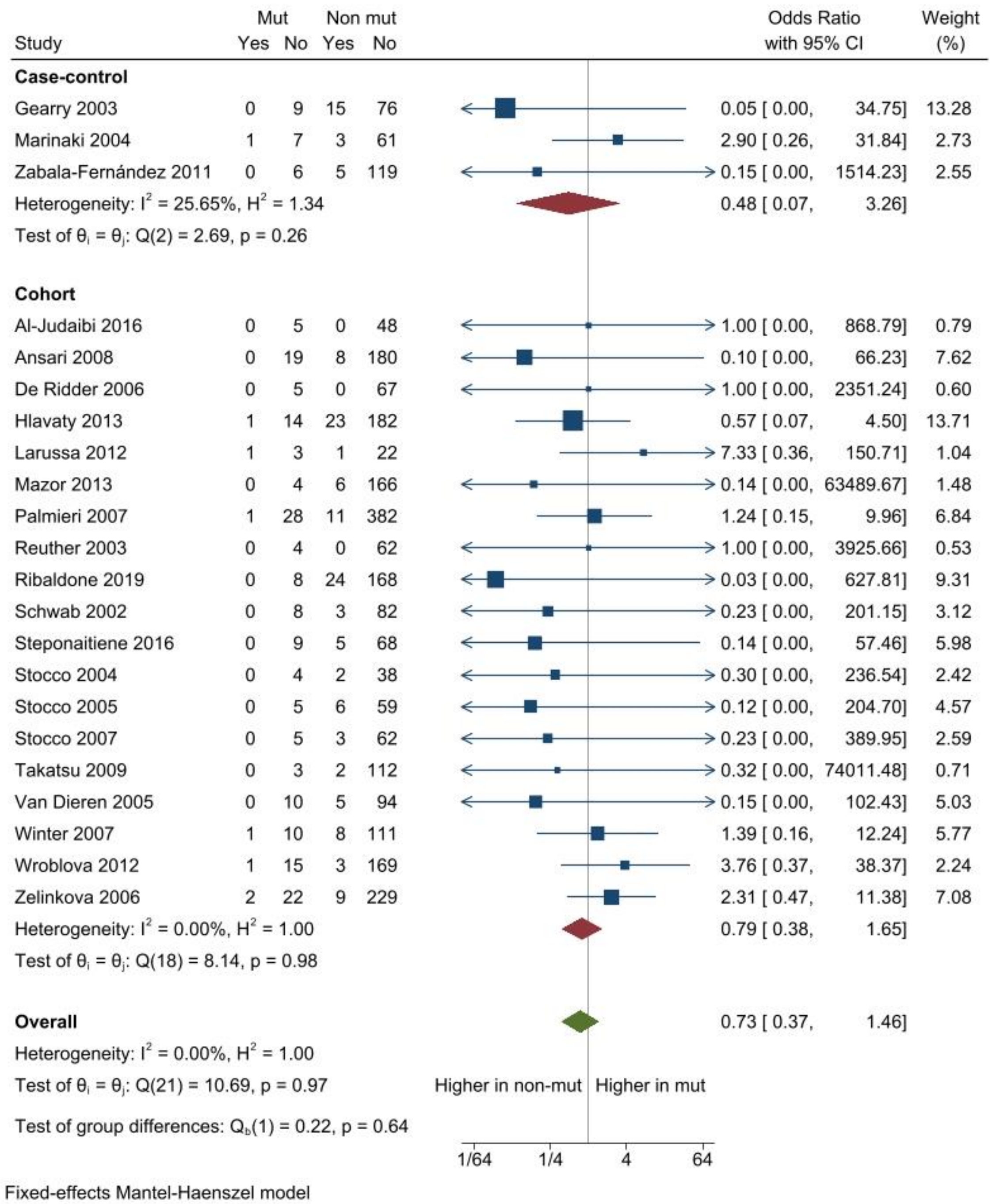


Figure S94. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *TPMT* vs wild-type, outcome: Hepatotoxicity

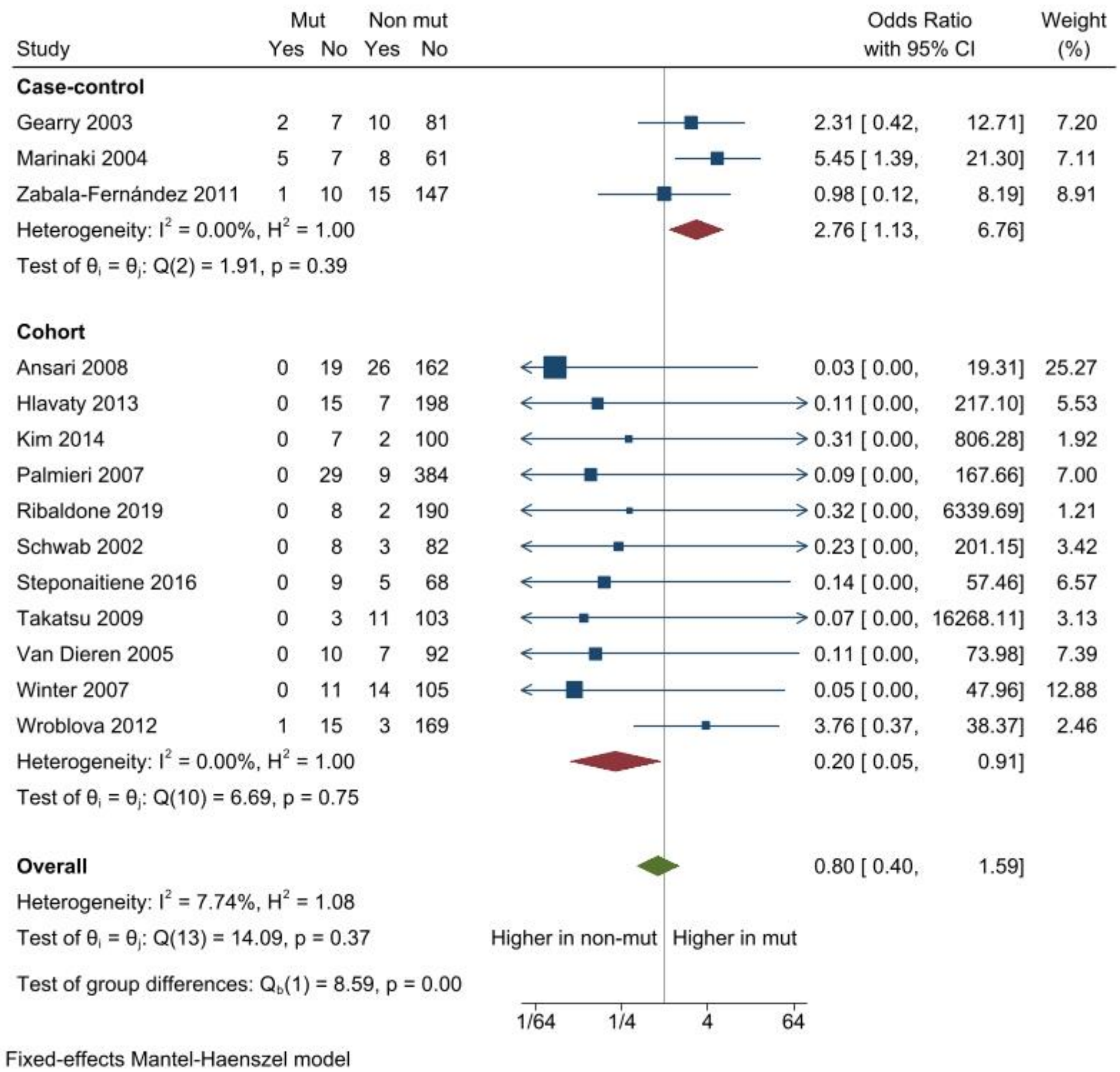


Figure S95. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *TPMT* vs wild-type, outcome: Gastrointestinal side effects

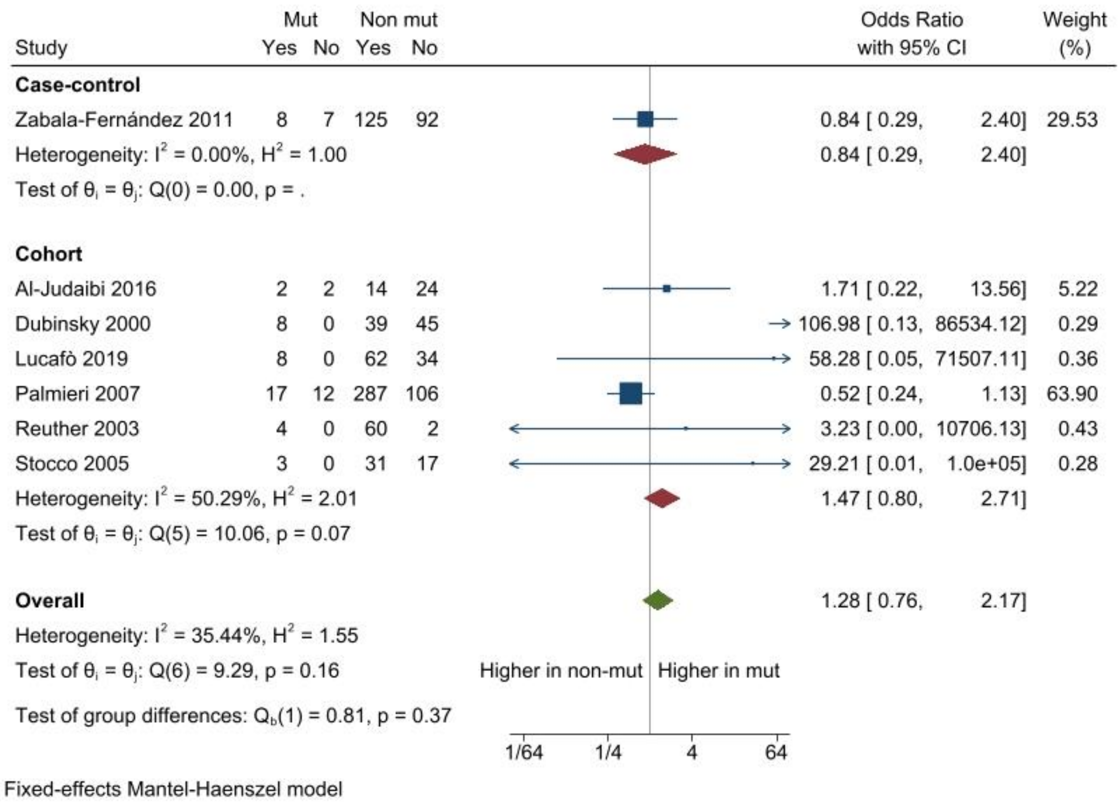


Figure S96. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *TPMT* vs wild-type, outcome: Clinical remission

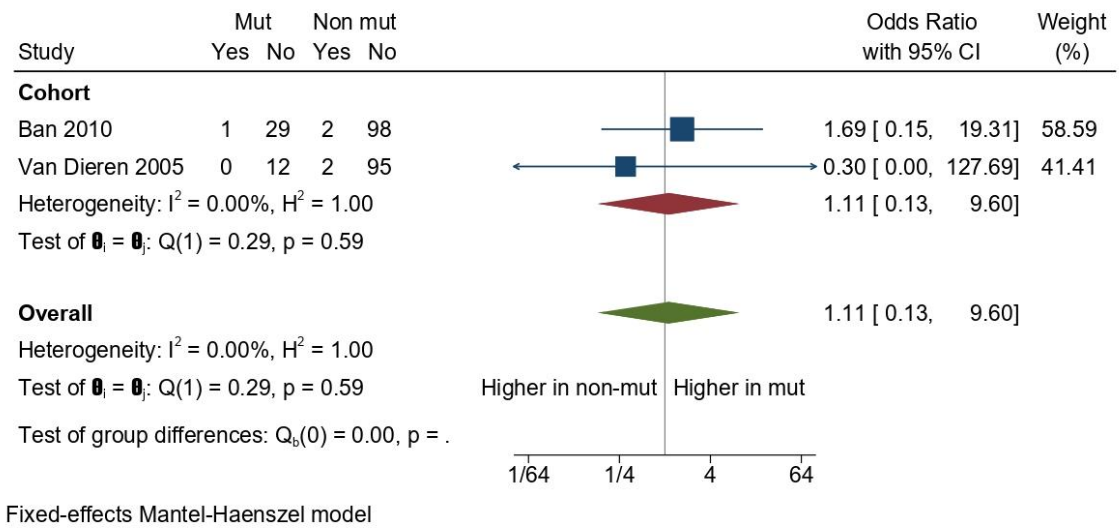


Figure S97. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Serious hematologic AE

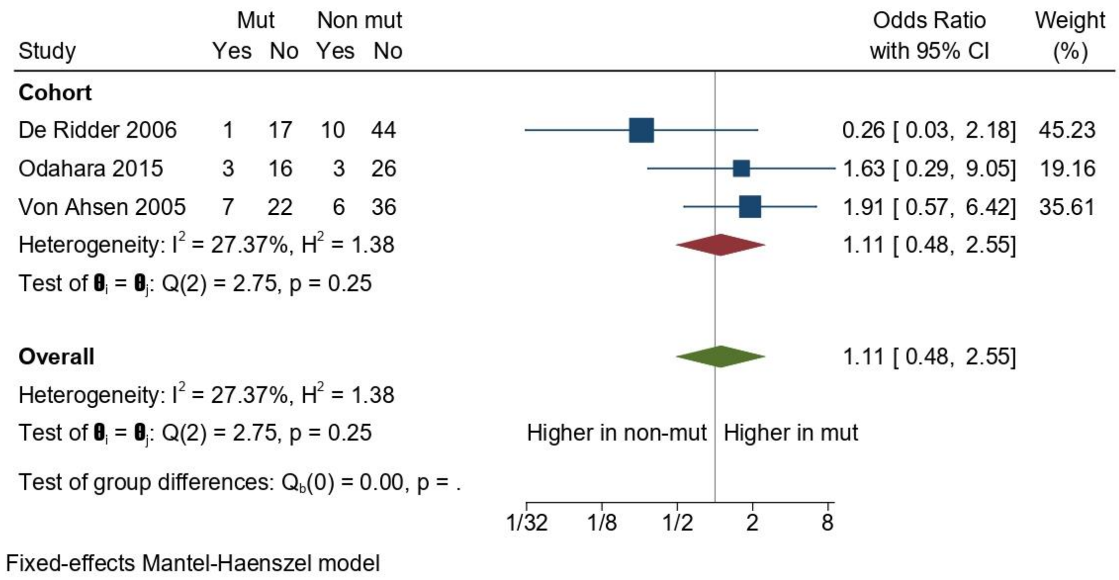


Figure S98. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Withdrawal due to AE

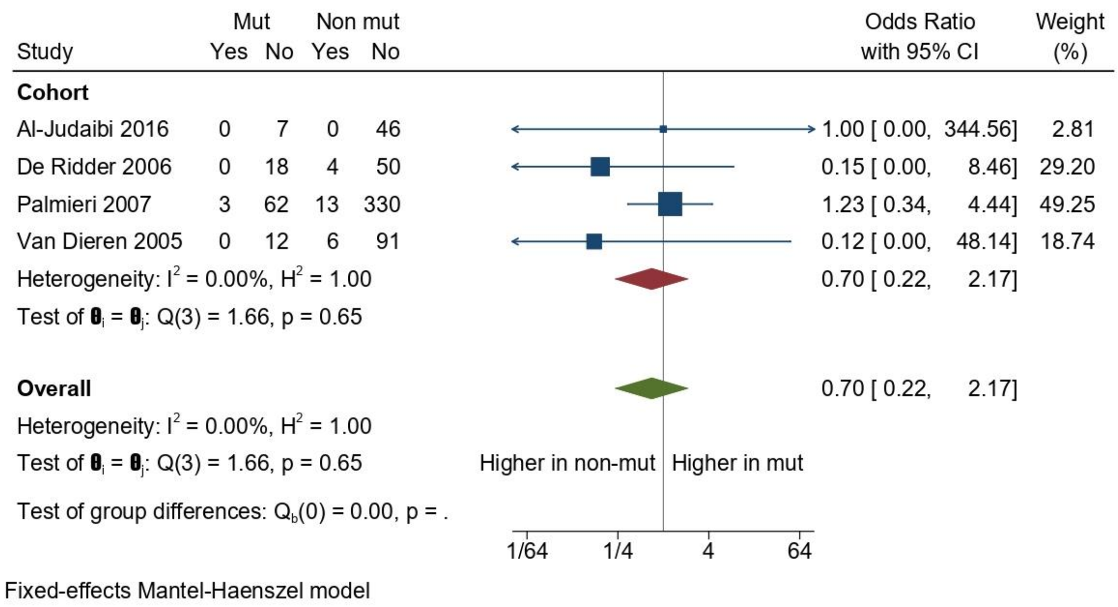


Figure S99. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Pancreatitis

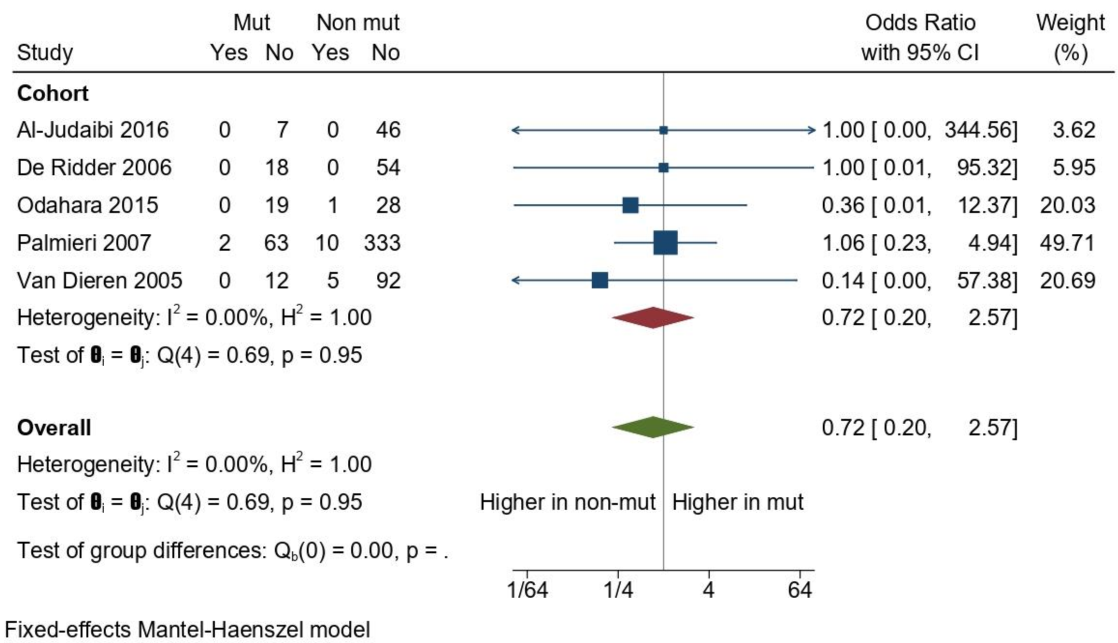


Figure S100. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Hepatotoxicity

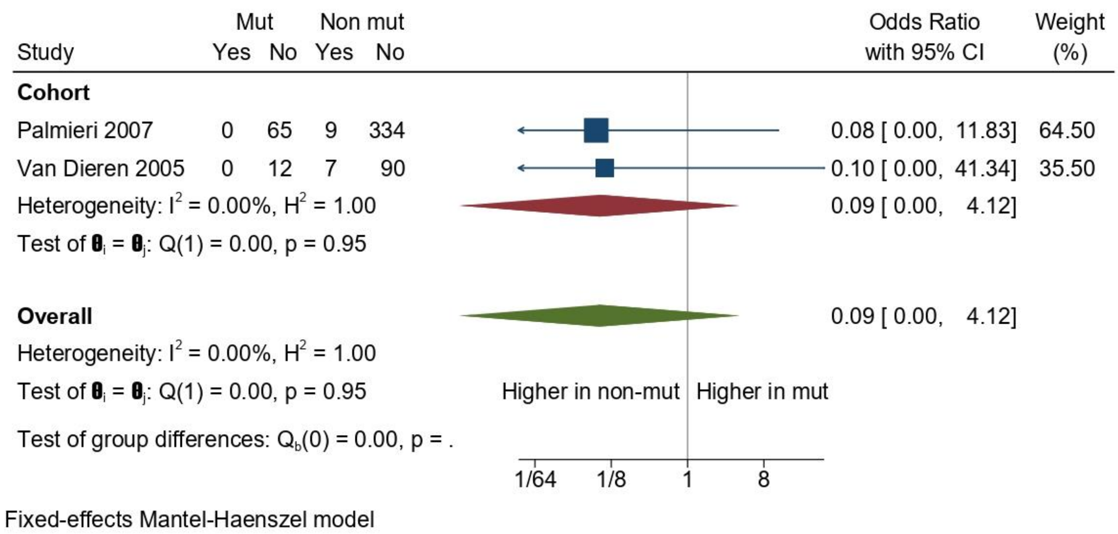


Figure S101. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Gastrointestinal side effects

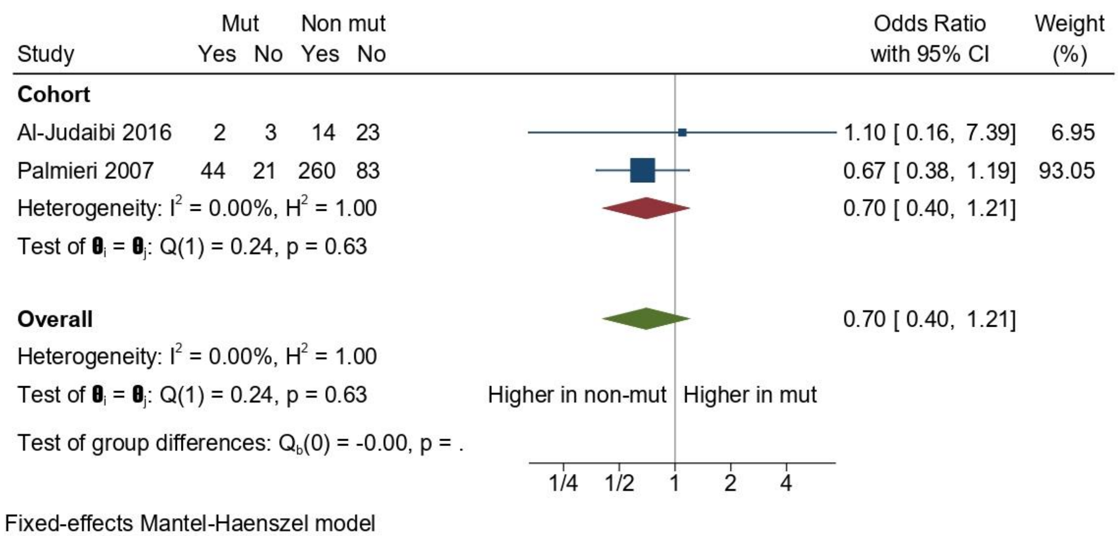


Figure S102. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Clinical remission

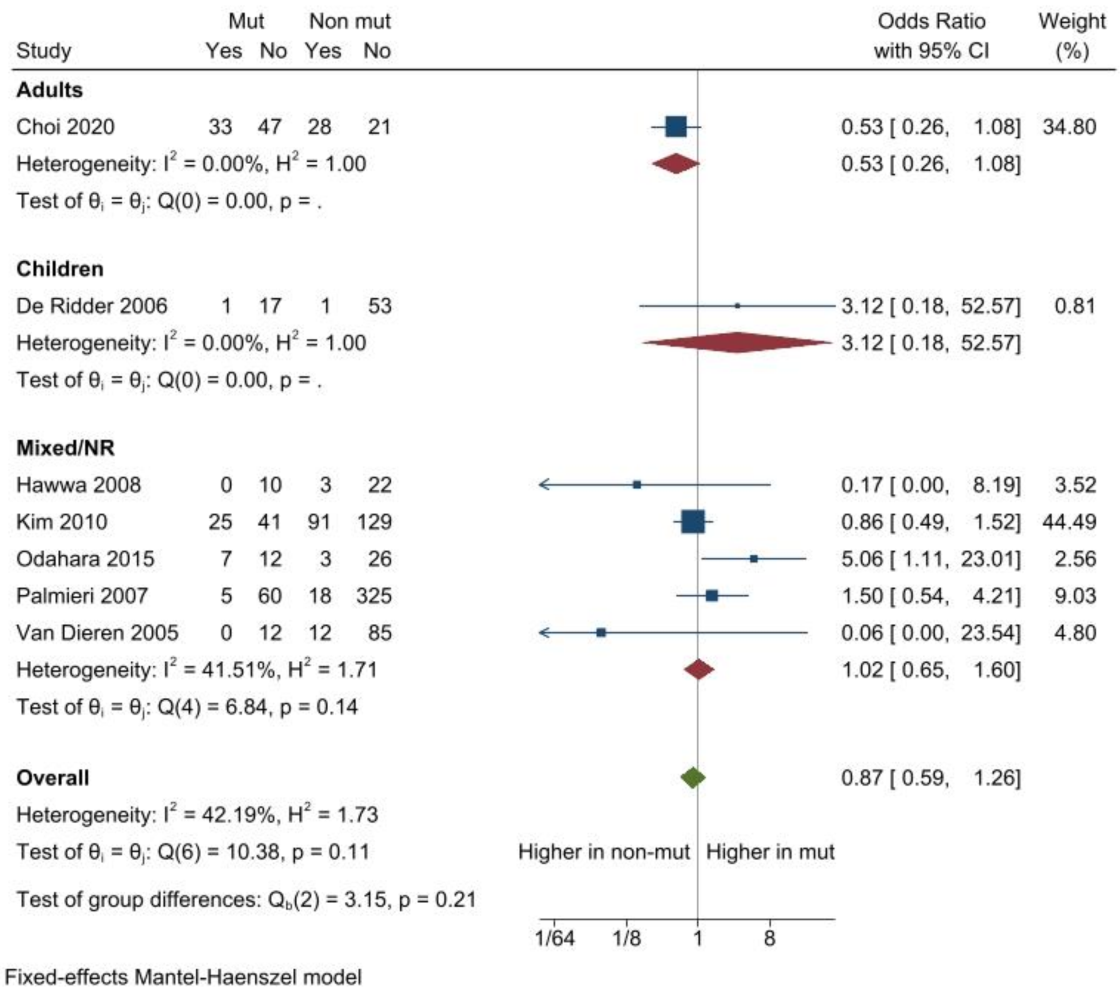


Figure S103. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Total hematologic AE. Subgroup analysis according to age

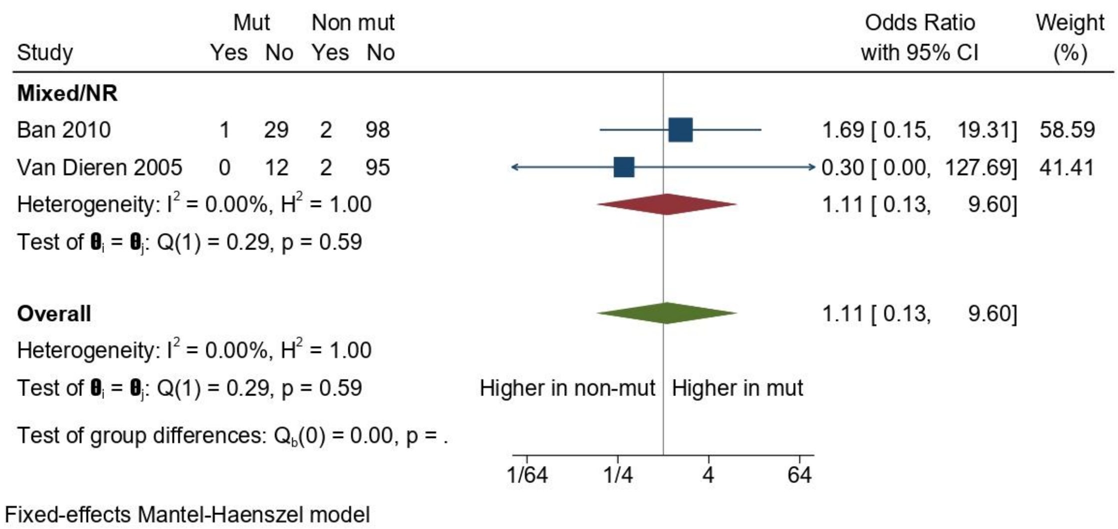


Figure S104. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Serious hematologic AE. Subgroup analysis according to age

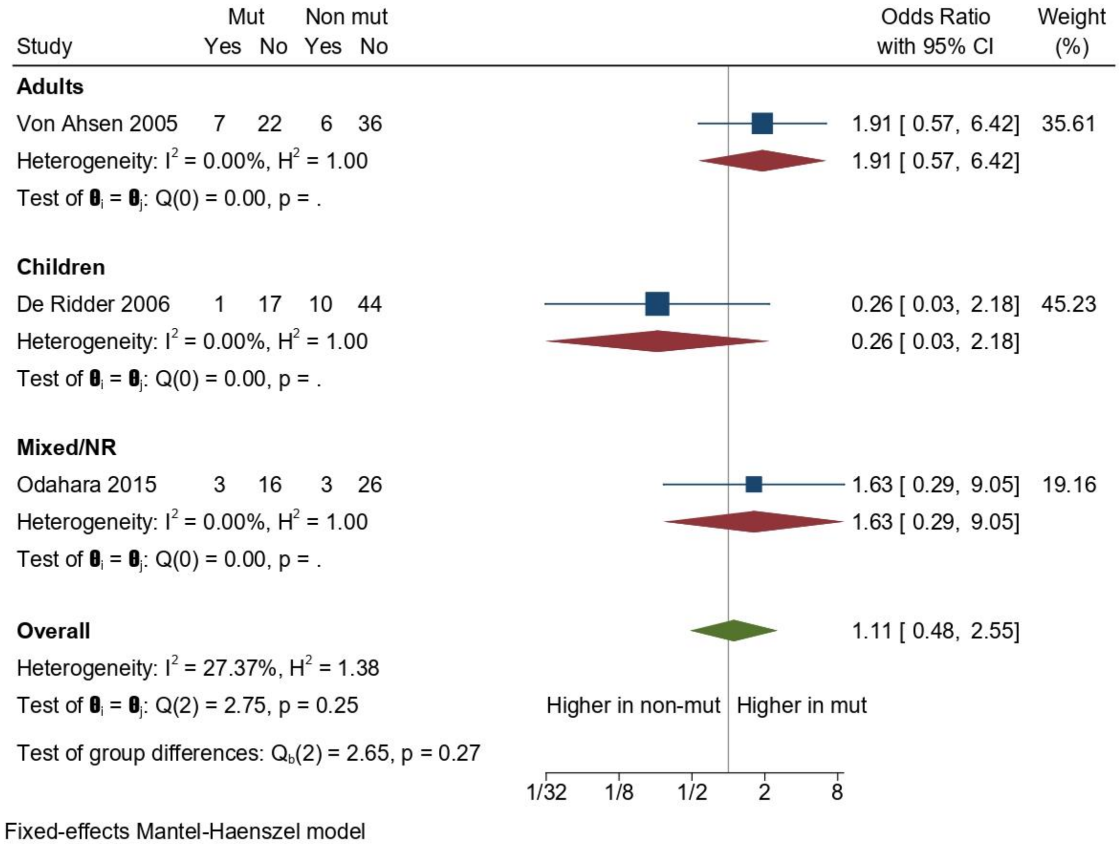


Figure S105. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Withdrawal due to AE. Subgroup analysis according to age

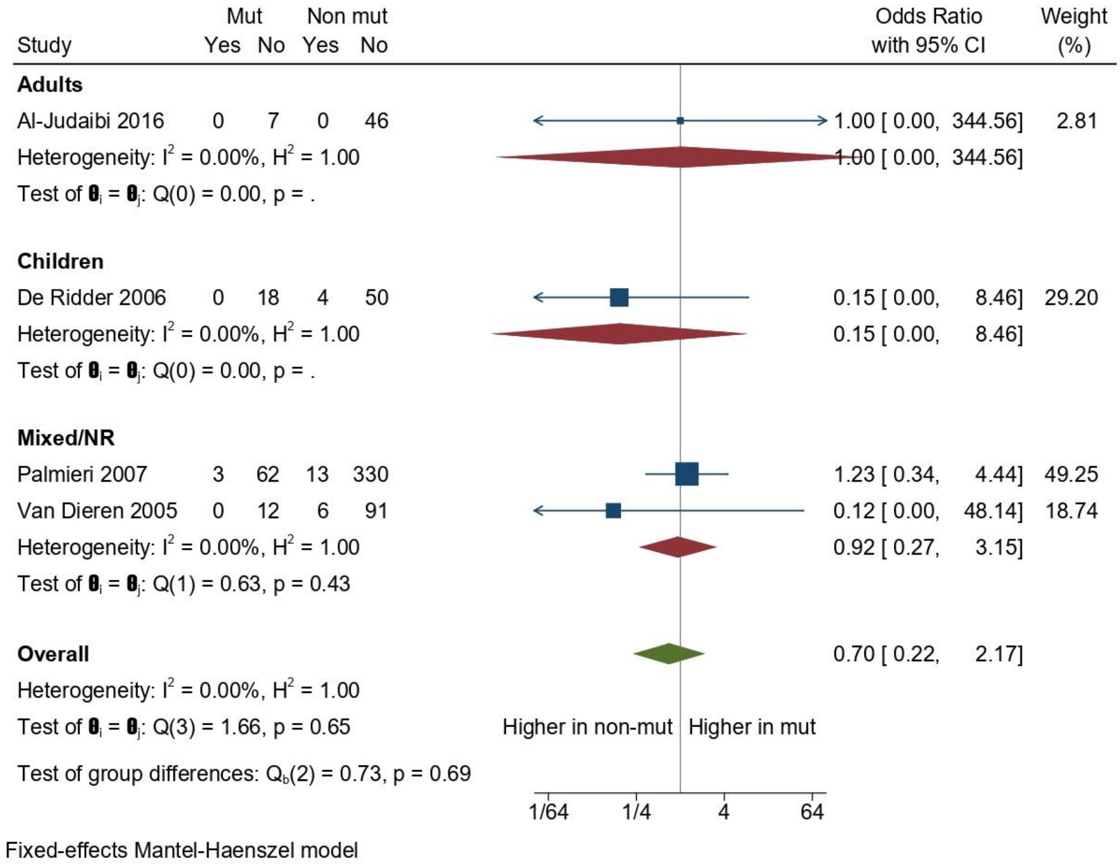


Figure S106. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Pancreatitis. Subgroup analysis according to age

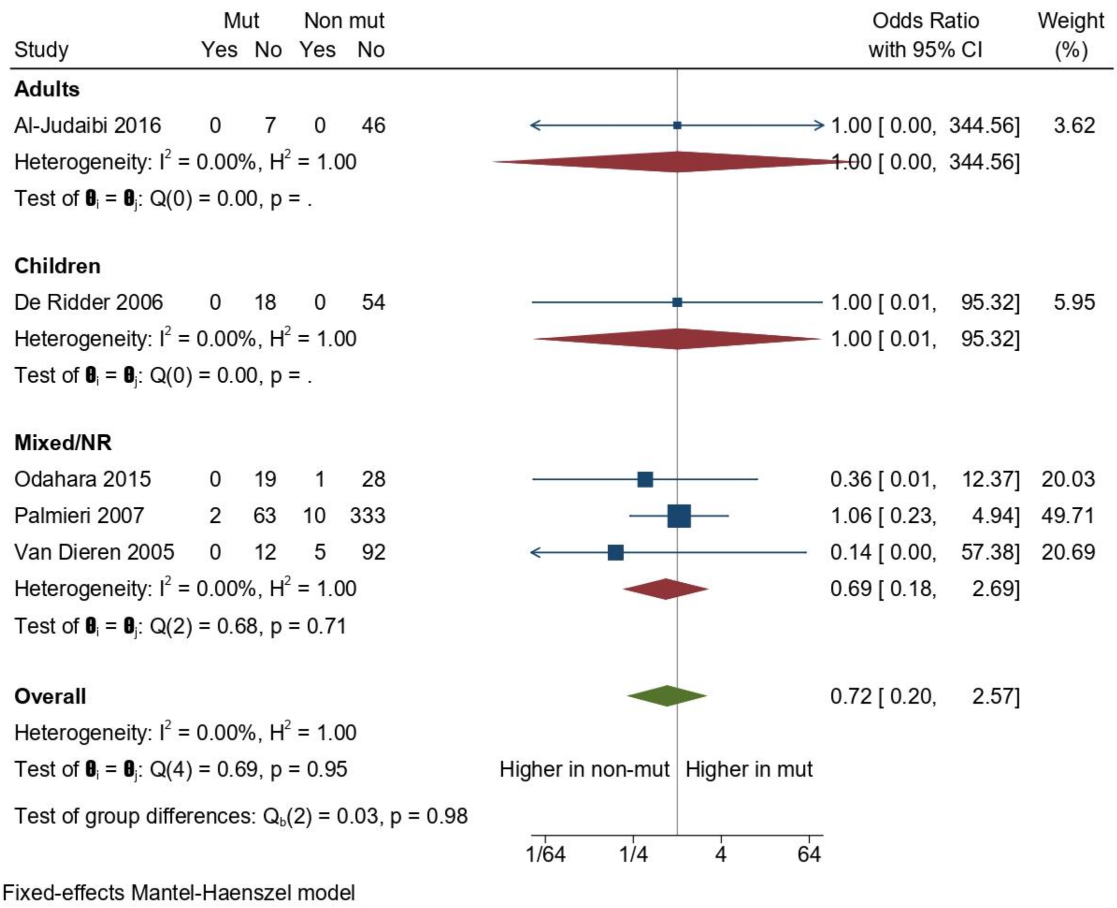


Figure S107. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Hepatotoxicity. Subgroup analysis according to age

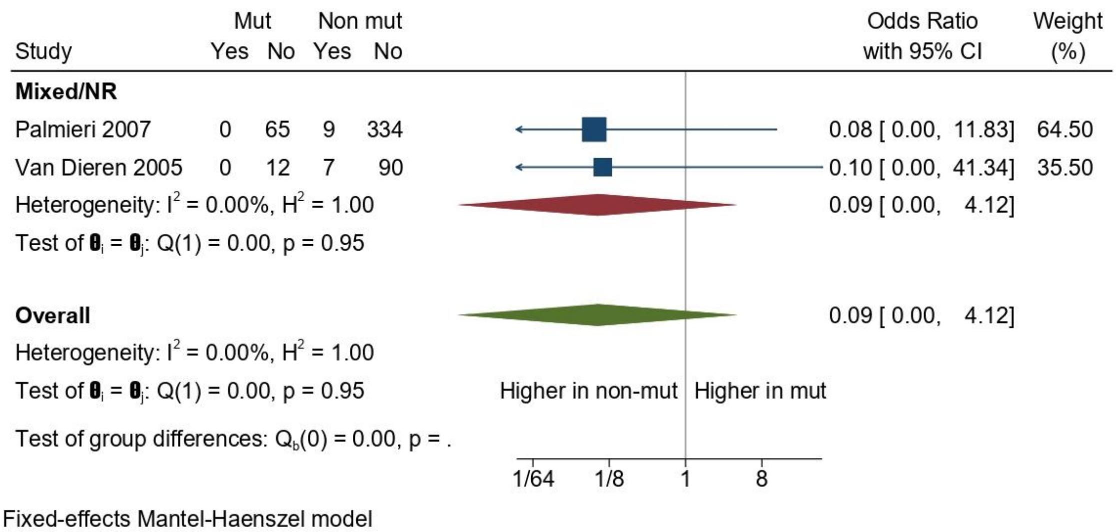


Figure S108. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Gastrointestinal side effects. Subgroup analysis according to age

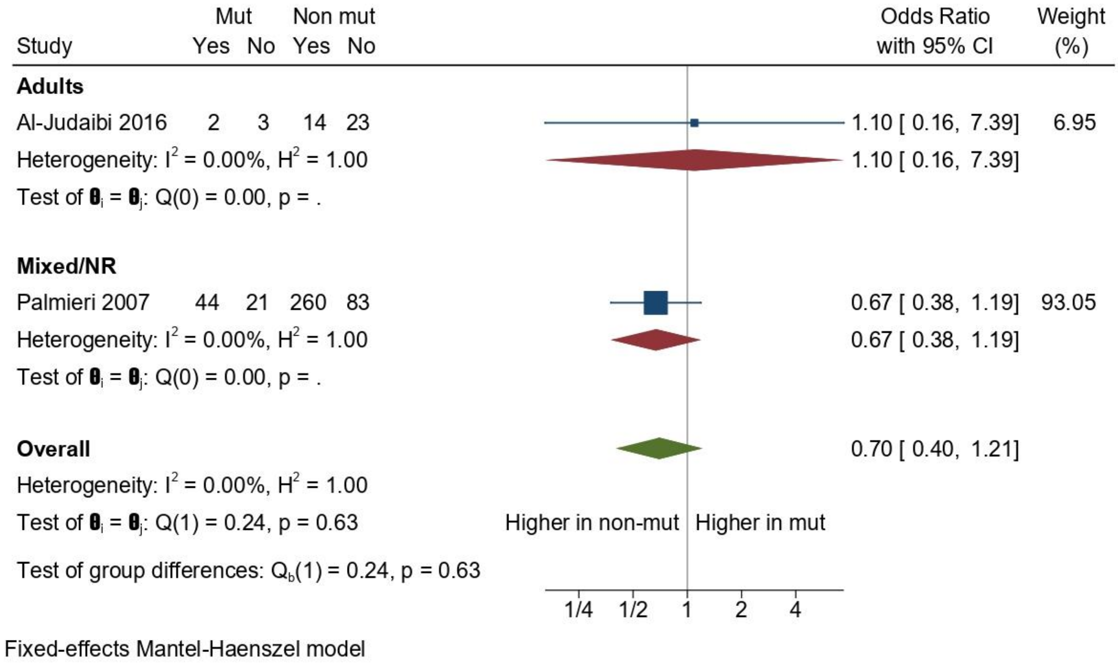


Figure S109. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Clinical remission. Subgroup analysis according to age

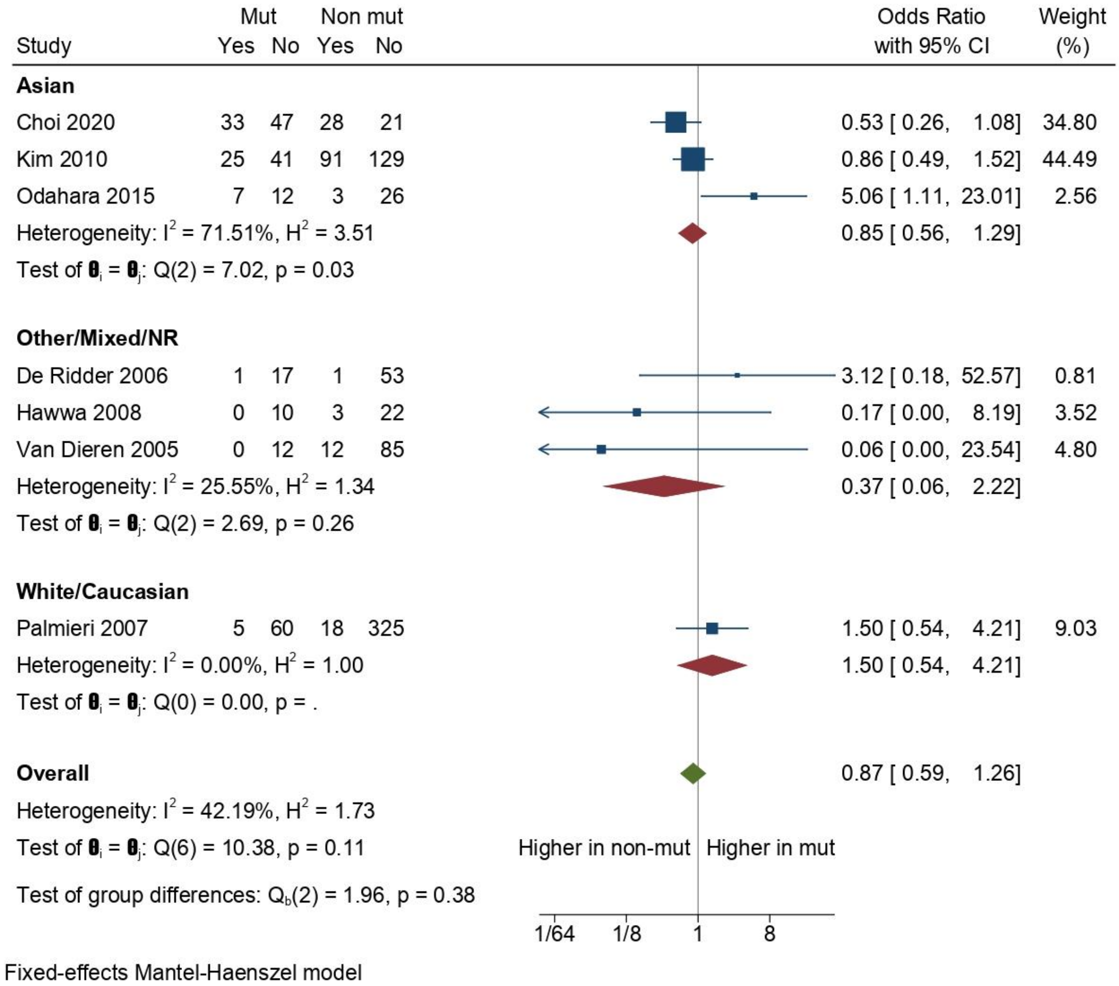


Figure S110. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Total hematologic AE. Subgroup analysis according to race

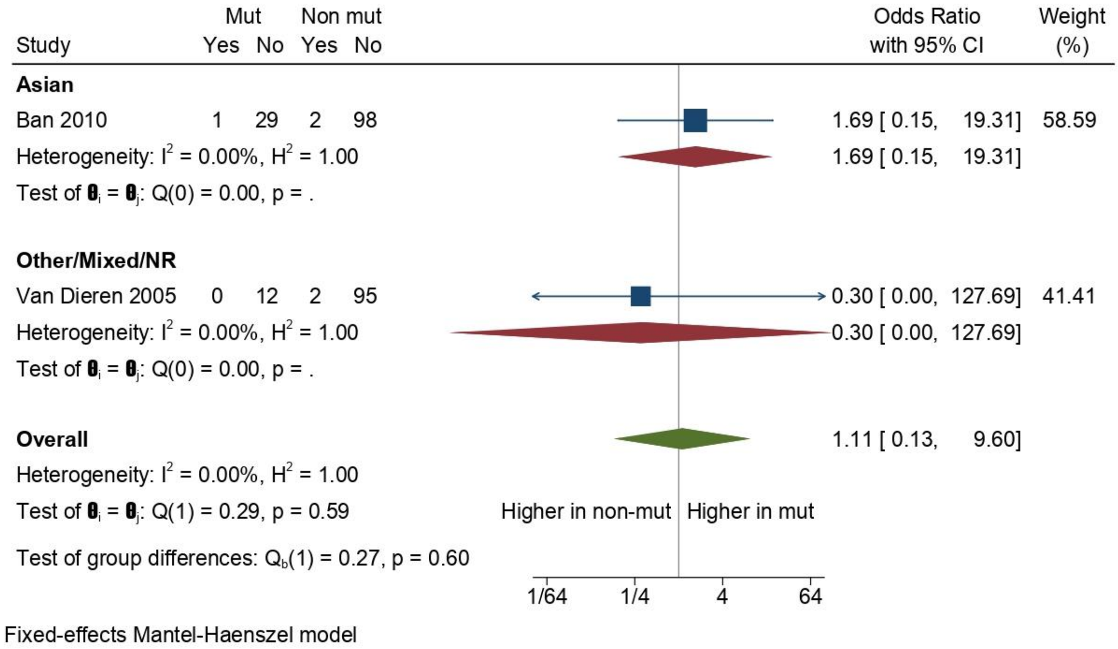


Figure S111. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Serious hematologic AE. Subgroup analysis according to race

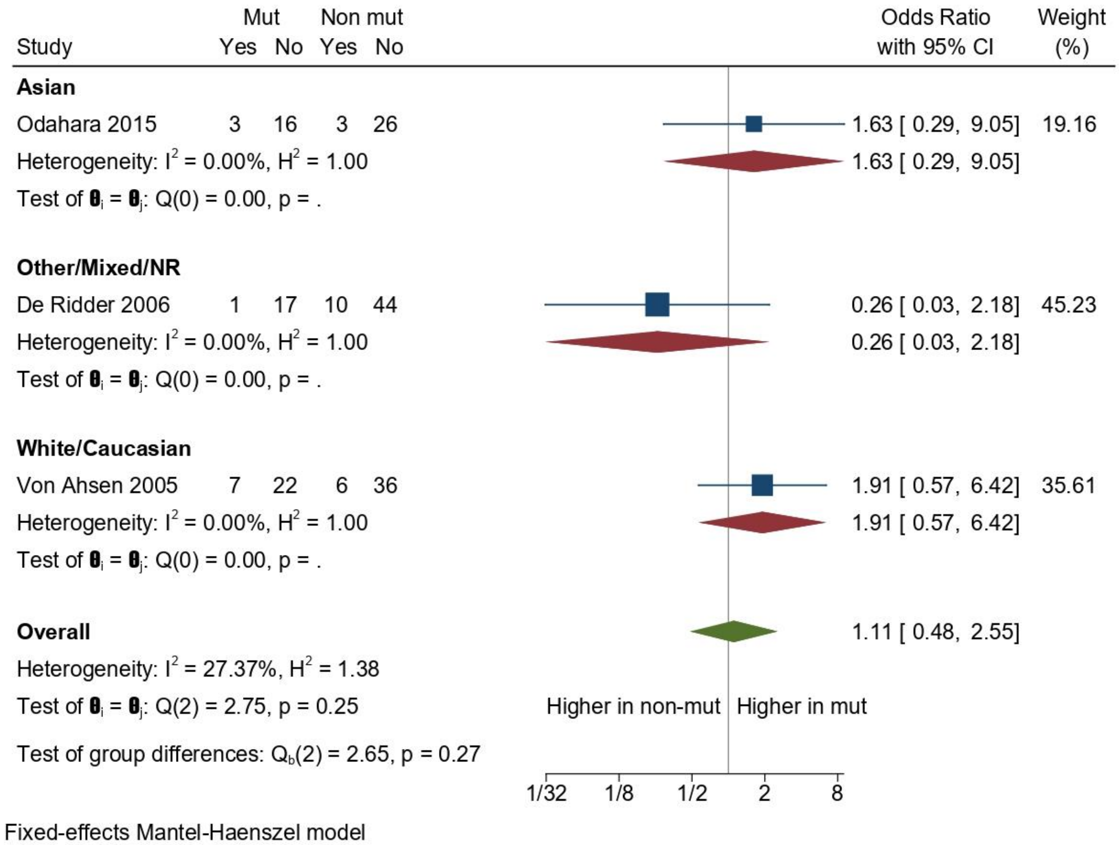


Figure S112. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Withdrawal due to AE. Subgroup analysis according to race

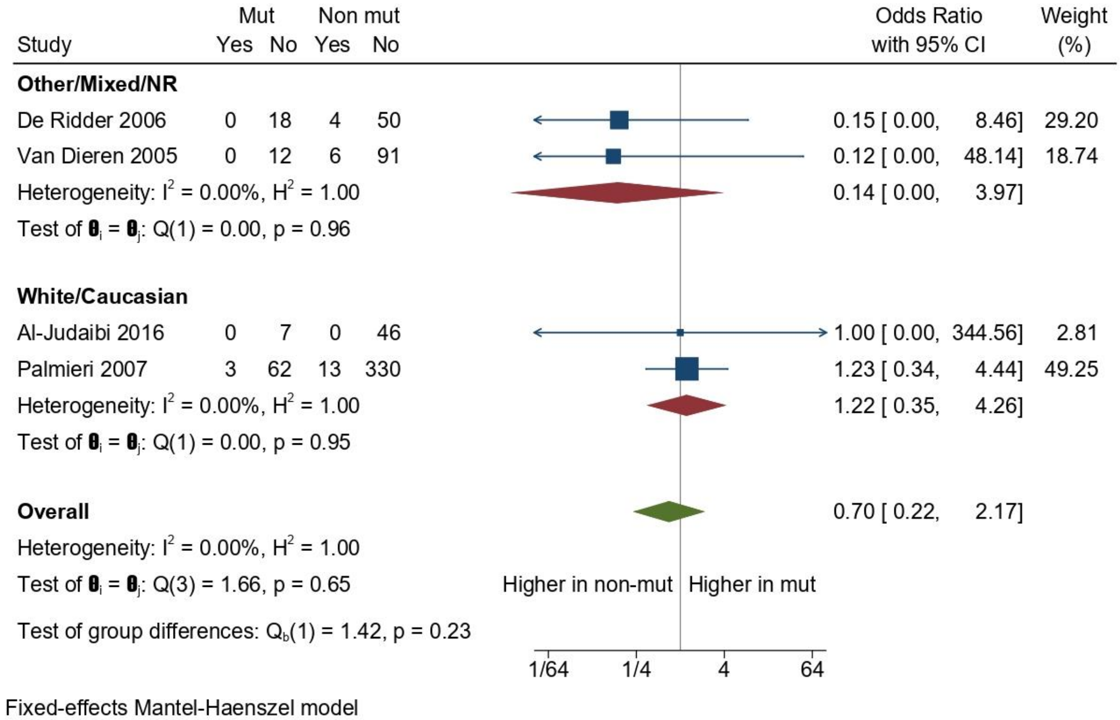


Figure S113. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Pancreatitis. Subgroup analysis according to race

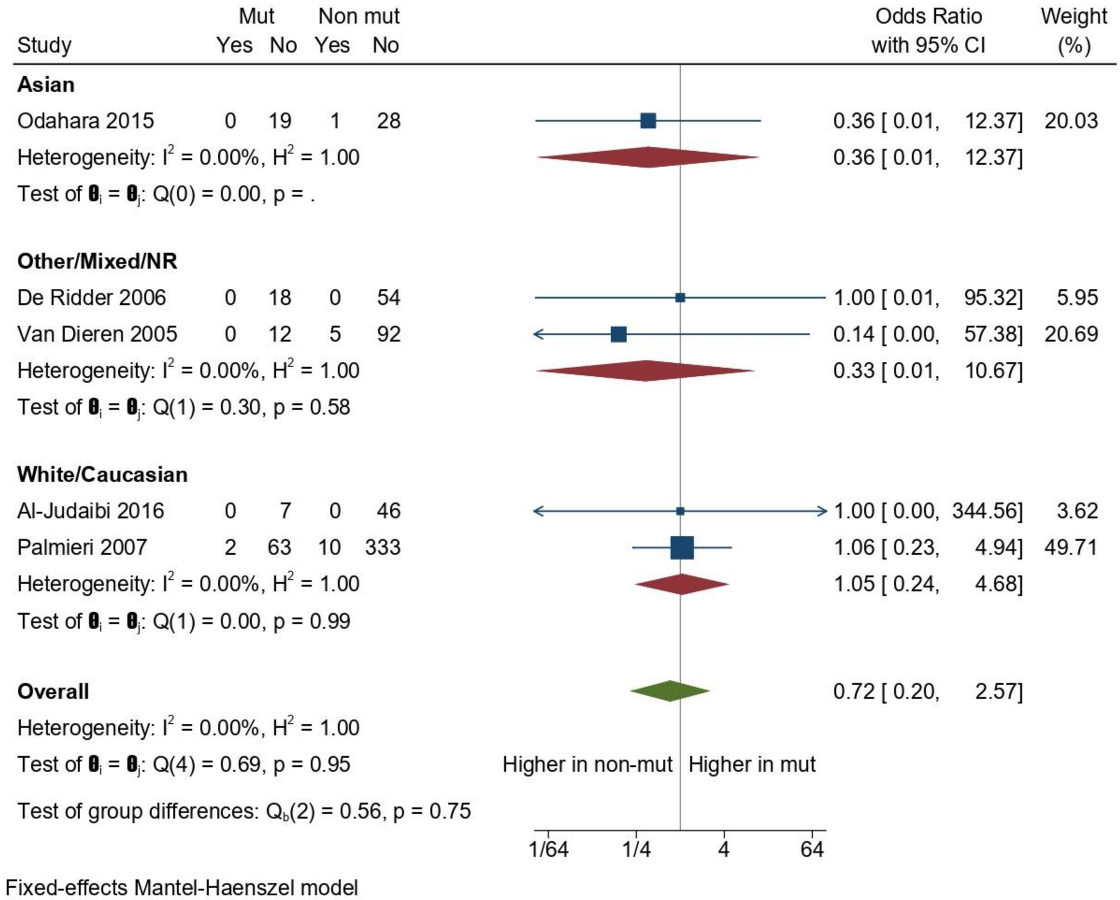


Figure S114. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Hepatotoxicity. Subgroup analysis according to race

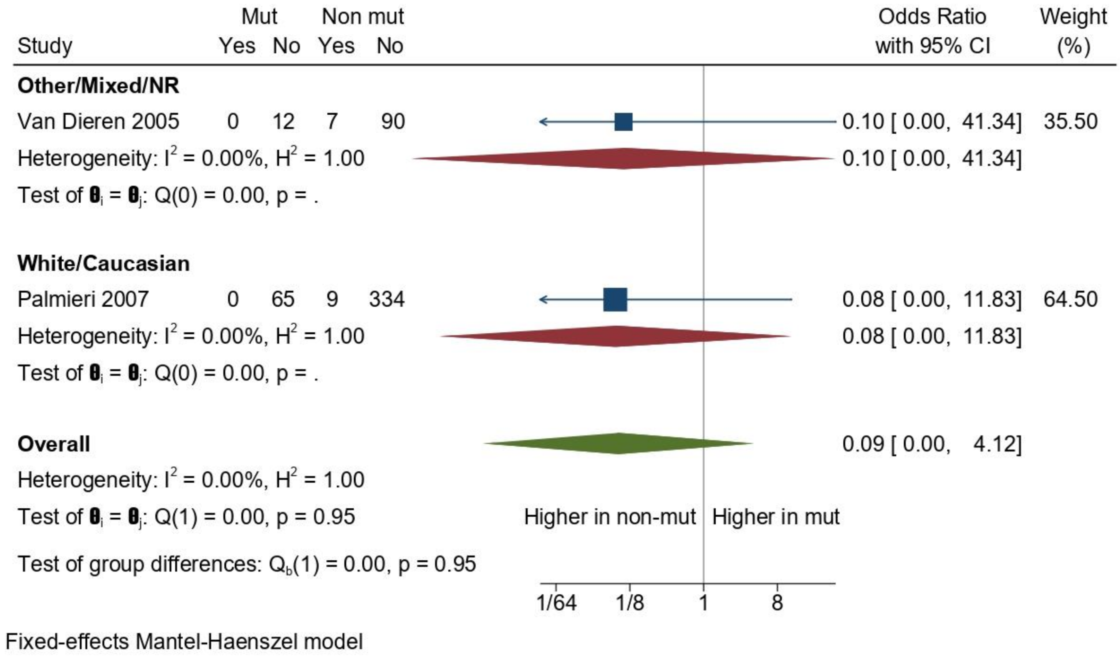


Figure S115. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Gastrointestinal side effects. Subgroup analysis according to race

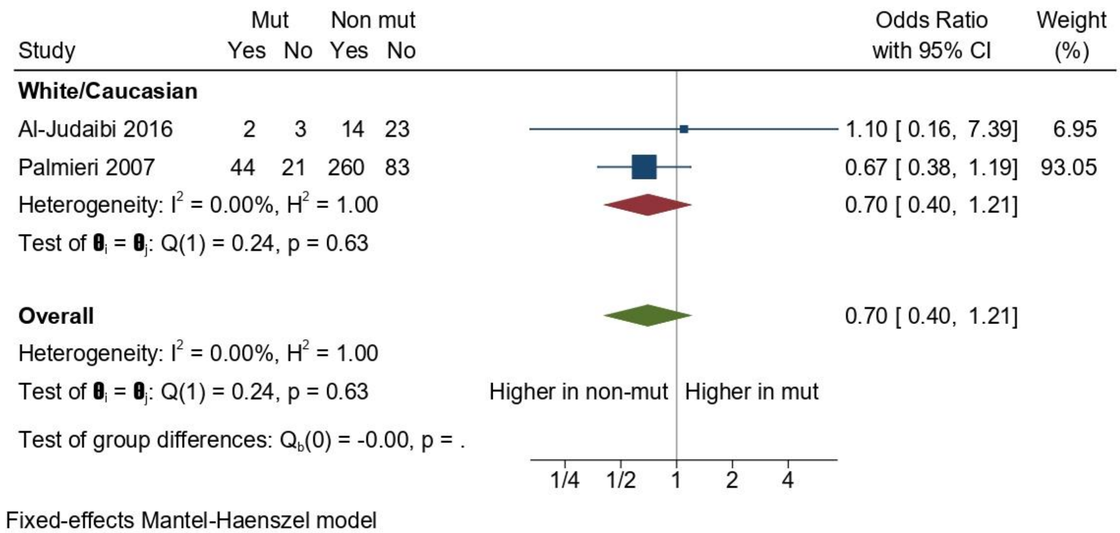


Figure S116. Forest plot of comparison mutated *ITPA* vs wild-type *ITPA*, outcome: Clinical remission. Subgroup analysis according to race

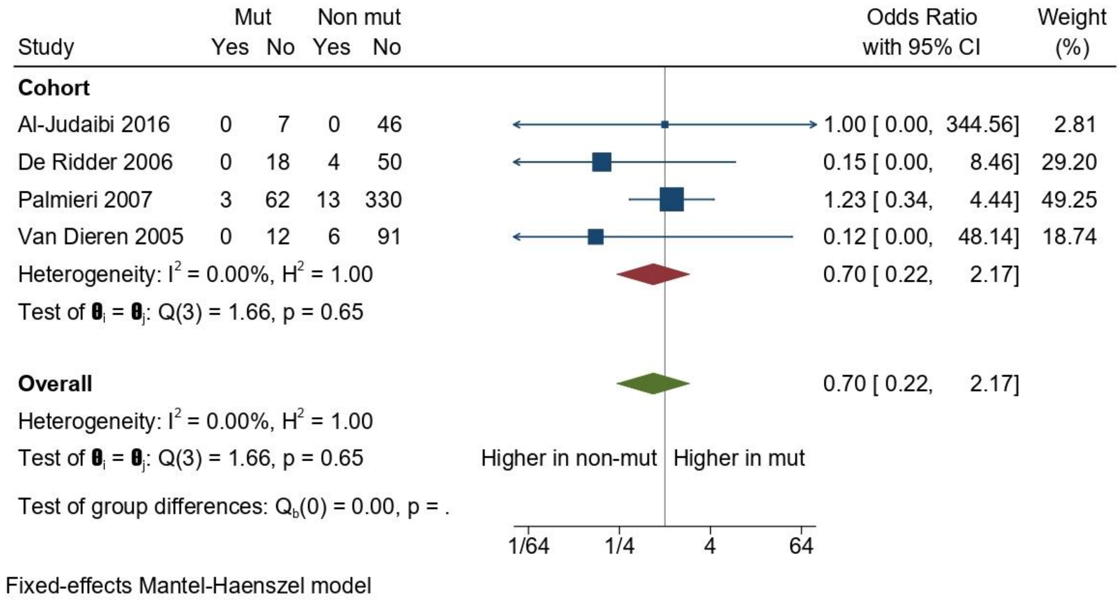


Figure S117. Forest plot of comparison heterozygous *ITPA* vs wild-type *ITPA*, outcome: Total hematologic adverse events

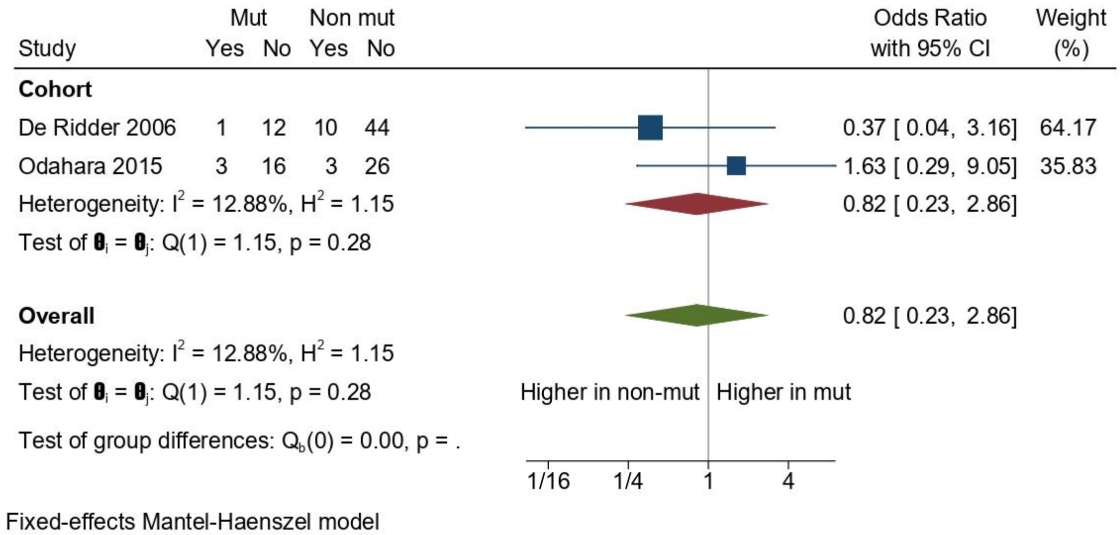


Figure S118. Forest plot of comparison heterozygous *ITPA* vs wild-type *ITPA*, outcome: Withdrawal due to AE

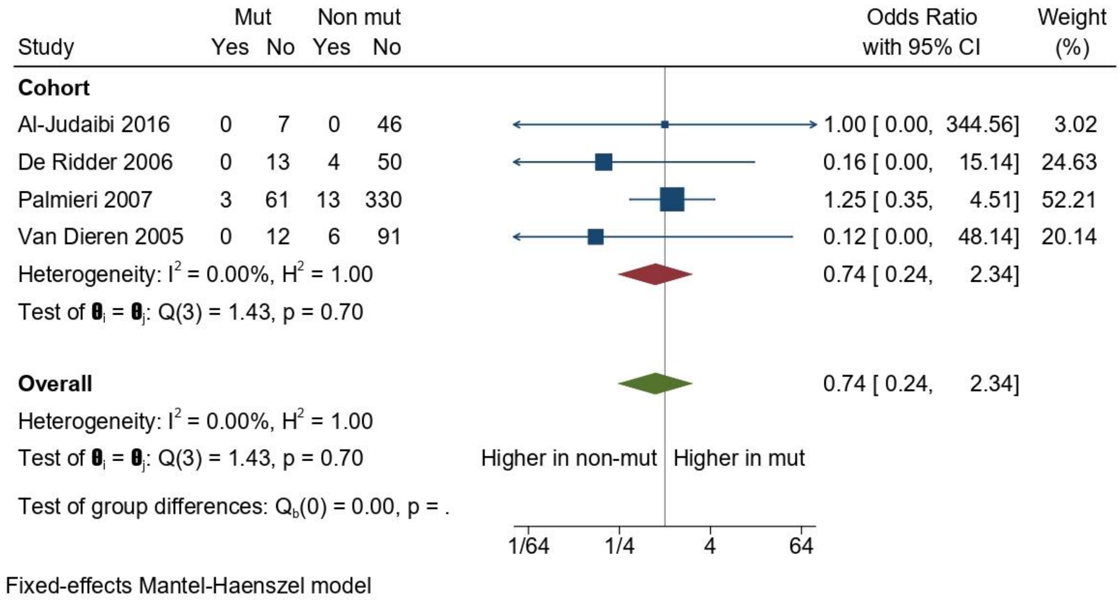


Figure S119. Forest plot of comparison heterozygous *ITPA* vs wild-type *ITPA*, outcome: Pancreatitis

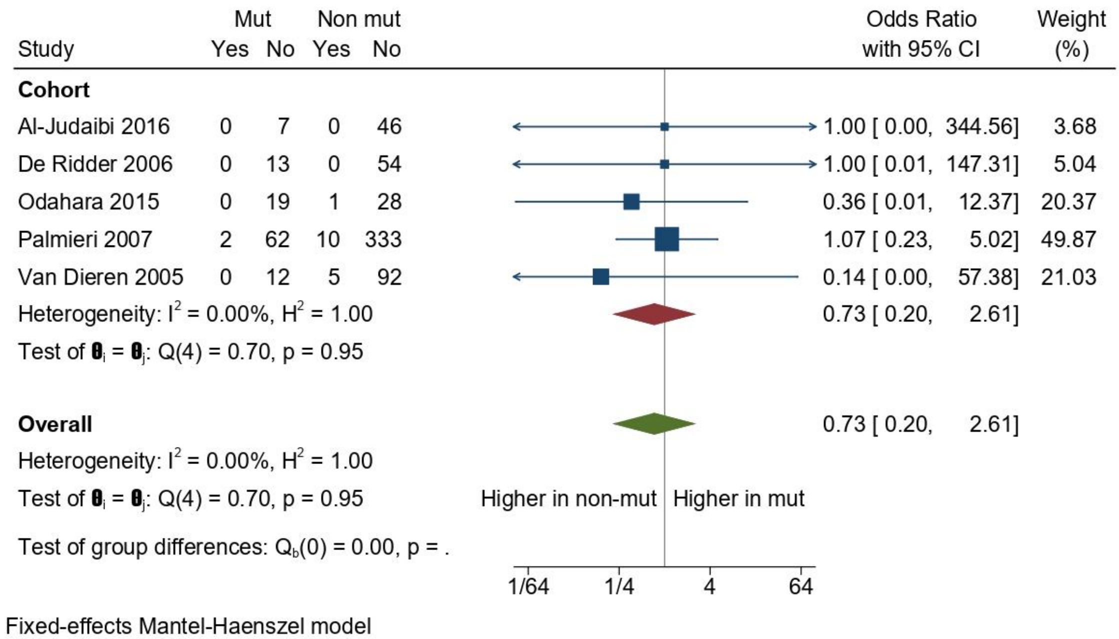


Figure S120. Forest plot of comparison heterozygous *ITPA* vs wild-type *ITPA*, outcome: Hepatotoxicity

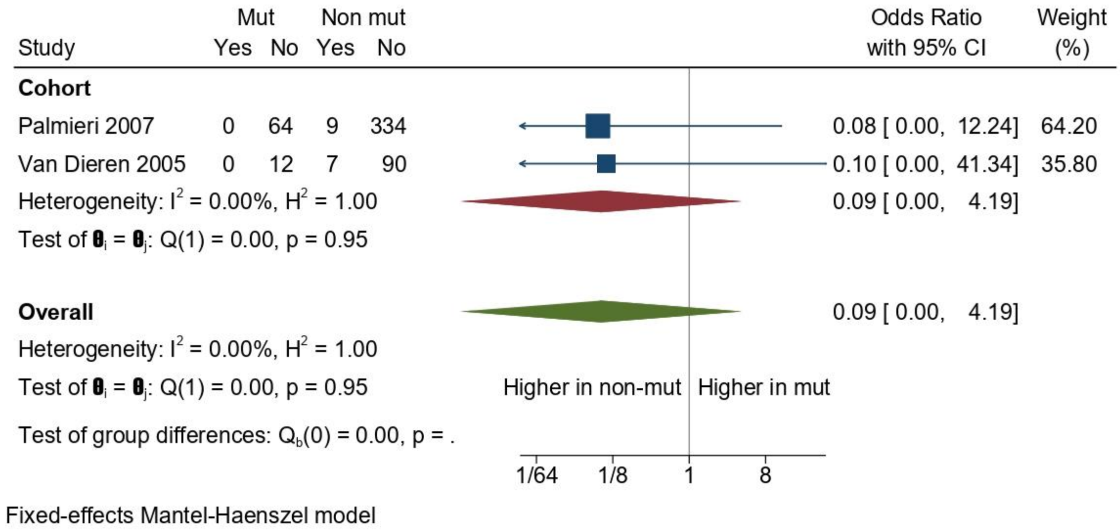


Figure S121. Forest plot of comparison heterozygous *ITPA* vs wild-type *ITPA*, outcome: Gastrointestinal side effects

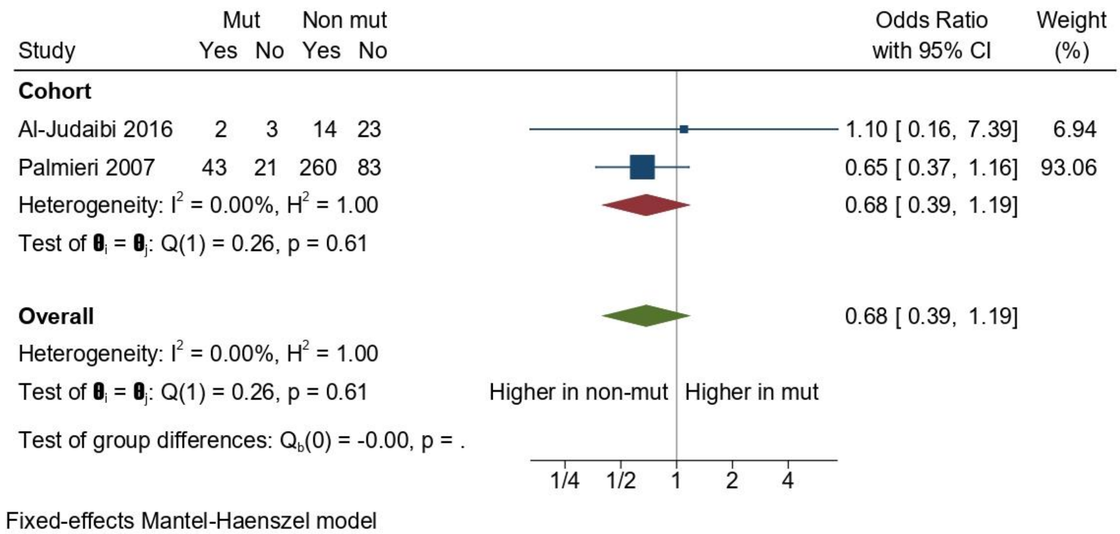


Figure S122. Forest plot of comparison heterozygous *ITPA* vs wild-type *ITPA*, outcome: Clinical remission

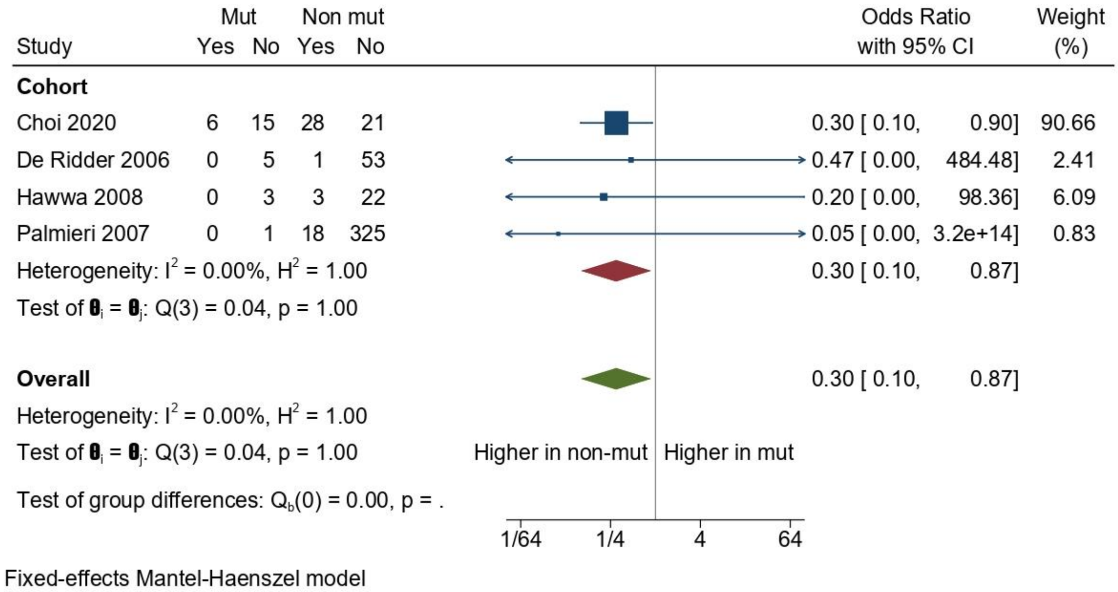


Figure S123. Forest plot of comparison 2 mutant *ITPA* alleles vs wild-type, outcome: Total hematologic adverse events

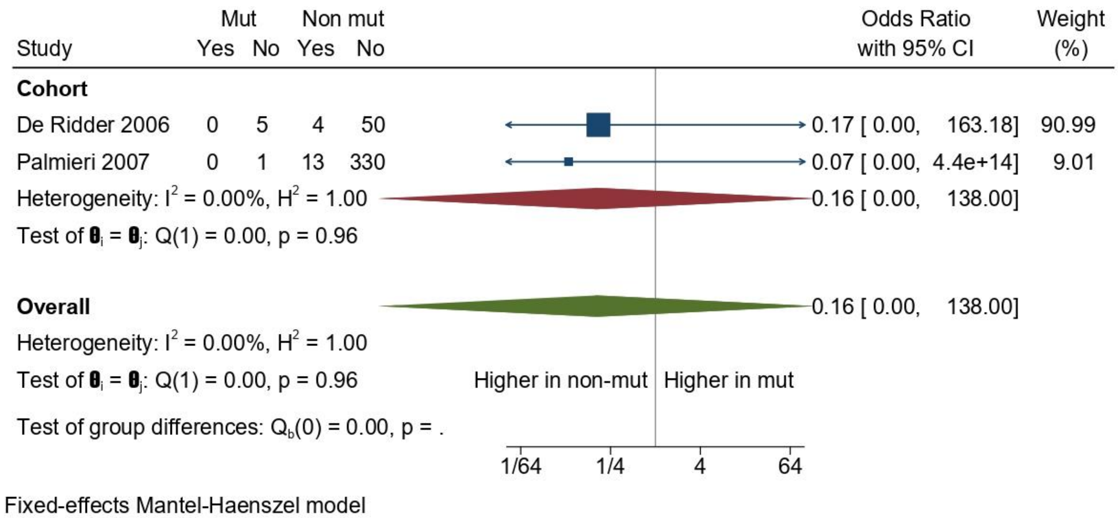


Figure S124. Forest plot of comparison 2 mutant *ITPA* alleles vs wild-type, outcome: Pancreatitis

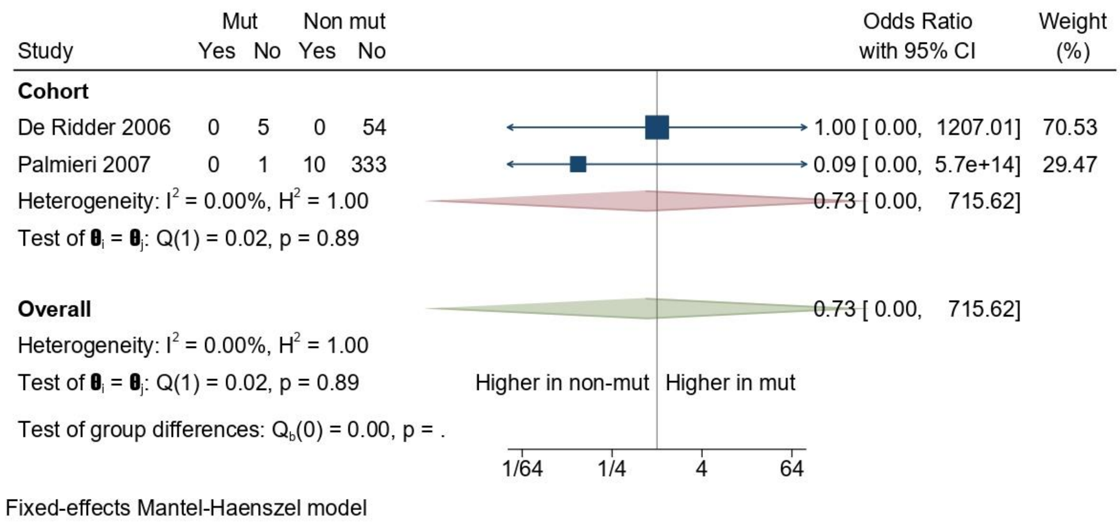


Figure S125. Forest plot of comparison 2 mutant *ITPA* alleles vs wild-type, outcome: Hepatotoxicity

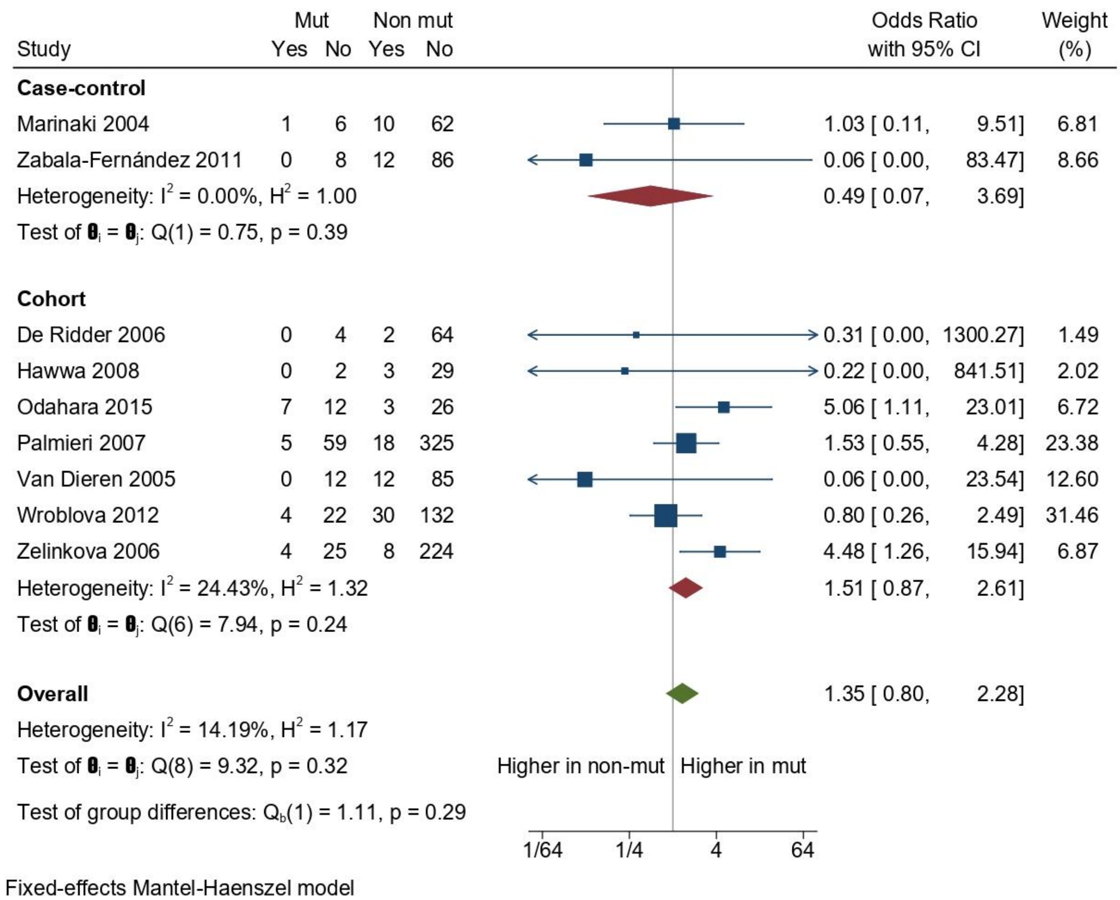


Figure S126. Forest plot of comparison *ITPA* 94C>A heterozygous vs wild-type, outcome: Total hematologic adverse events

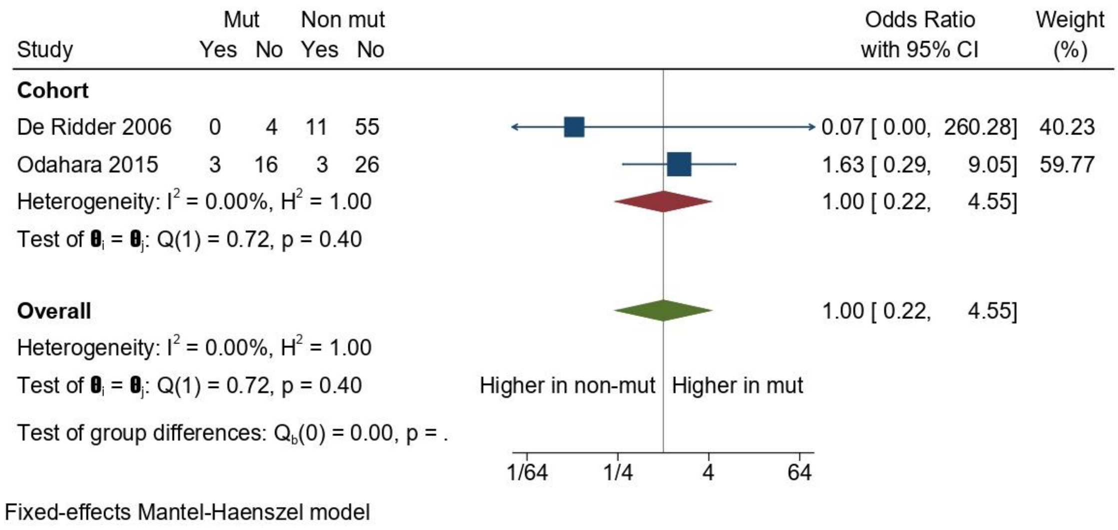


Figure S127. Forest plot of comparison *ITPA* 94C>A heterozygous vs wild-type, outcome: Withdrawal due to AE

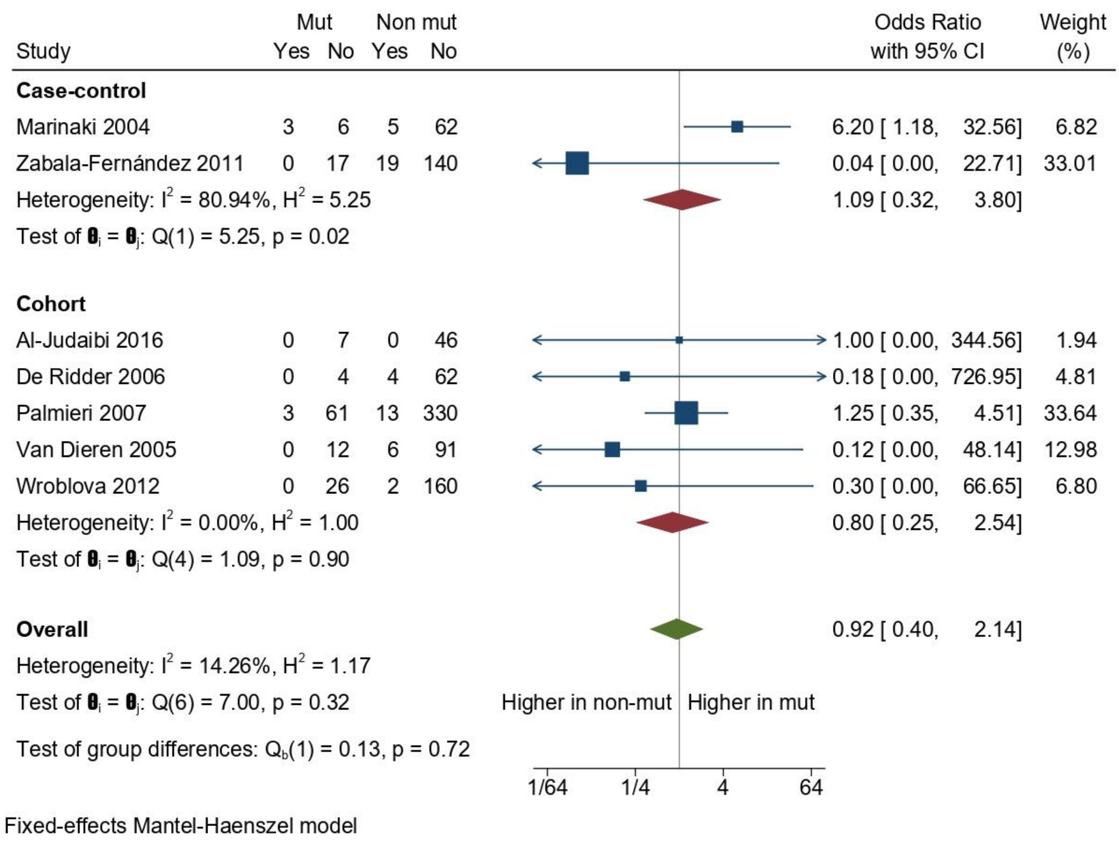


Figure S128. Forest plot of comparison *ITPA* 94C>A heterozygous vs wild-type, outcome: Pancreatitis

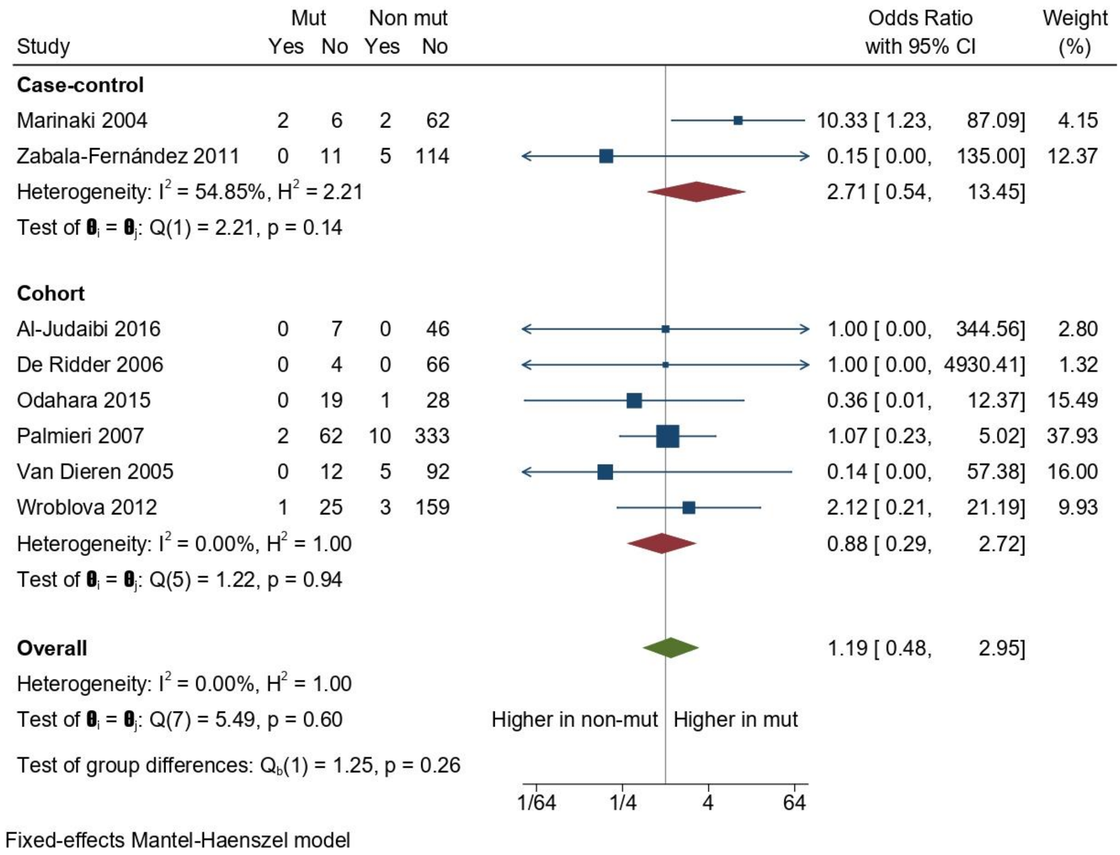


Figure S129. Forest plot of comparison *ITPA* 94C>A heterozygous vs wild-type, outcome: Hepatotoxicity

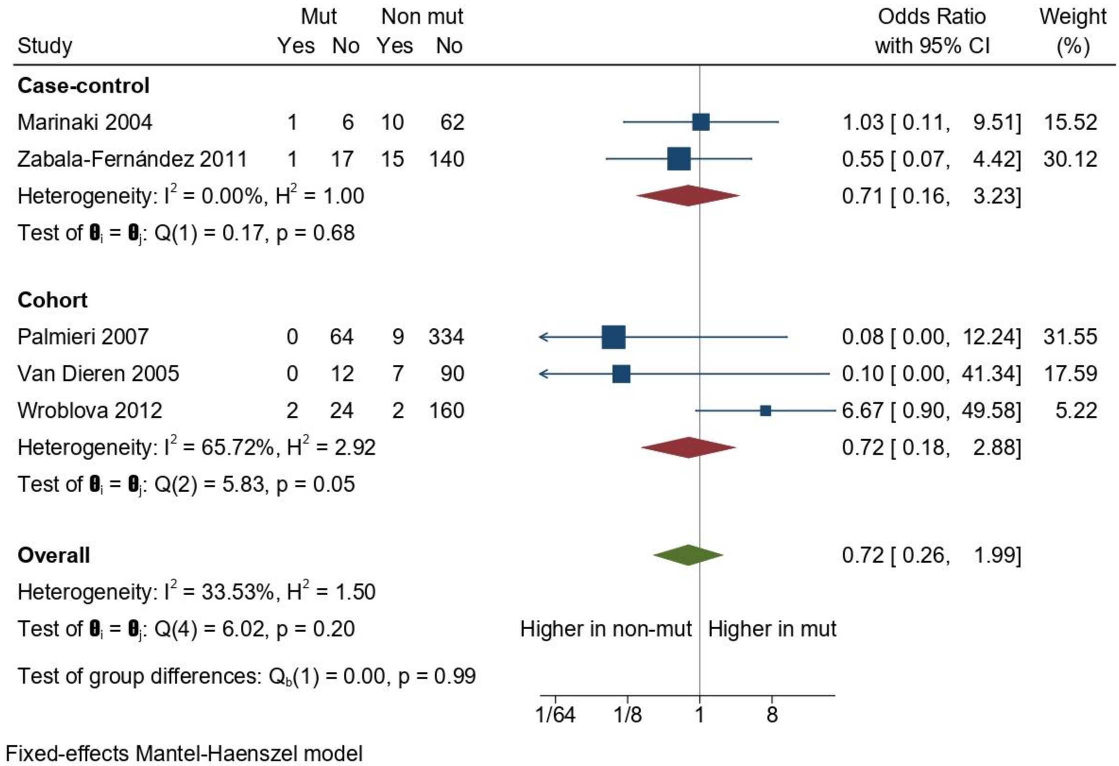


Figure S130. Forest plot of comparison *ITPA* 94C>A heterozygous vs wild-type, outcome: Gastrointestinal side effects

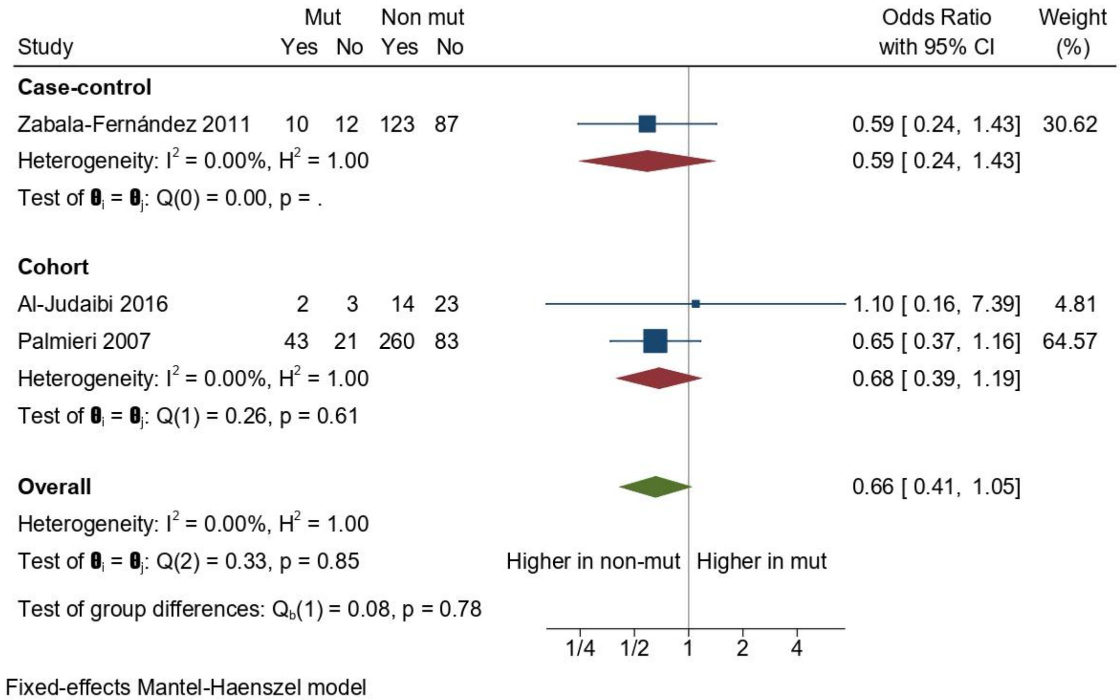


Figure S131. Forest plot of comparison *ITPA* 94C>A heterozygous vs wild-type, outcome: Clinical remission

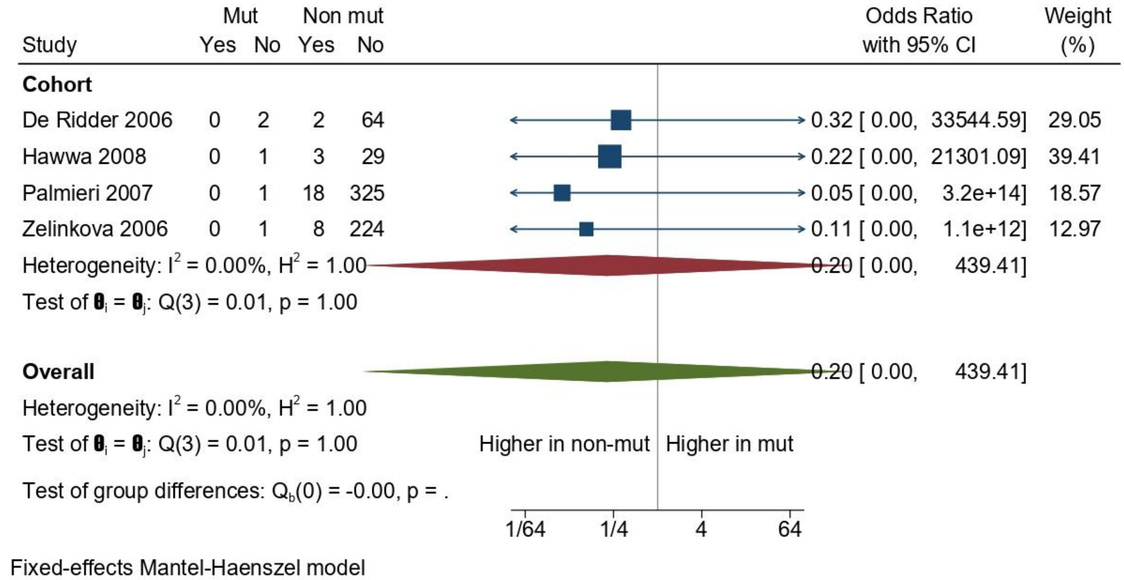


Figure S132. Forest plot of comparison *ITPA* 94C>A, 2 mutant alleles vs wild-type, outcome: Total hematologic adverse events

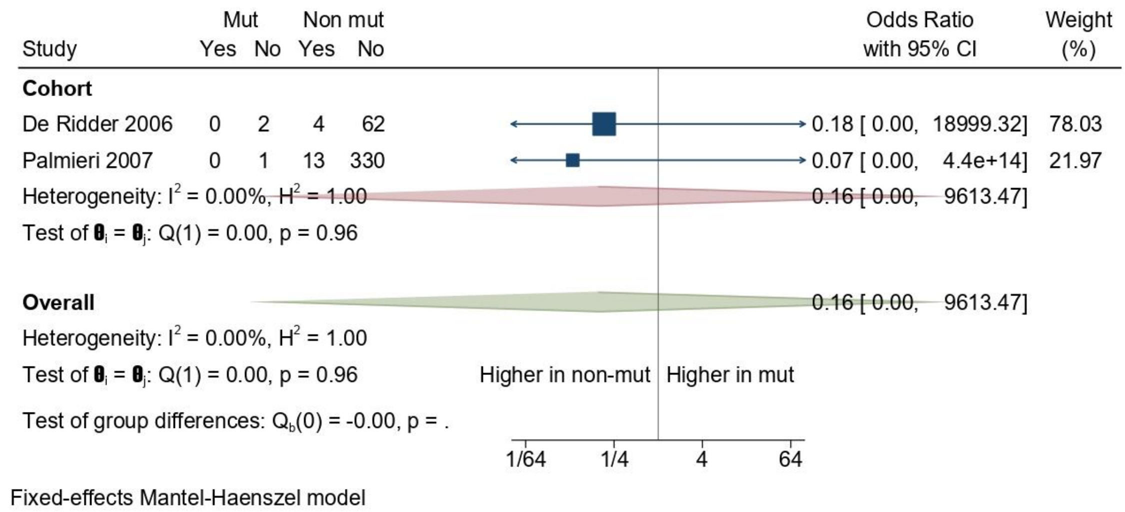


Figure S133. Forest plot of comparison *ITPA* 94C>A, 2 mutant alleles vs wild-type, outcome: Pancreatitis

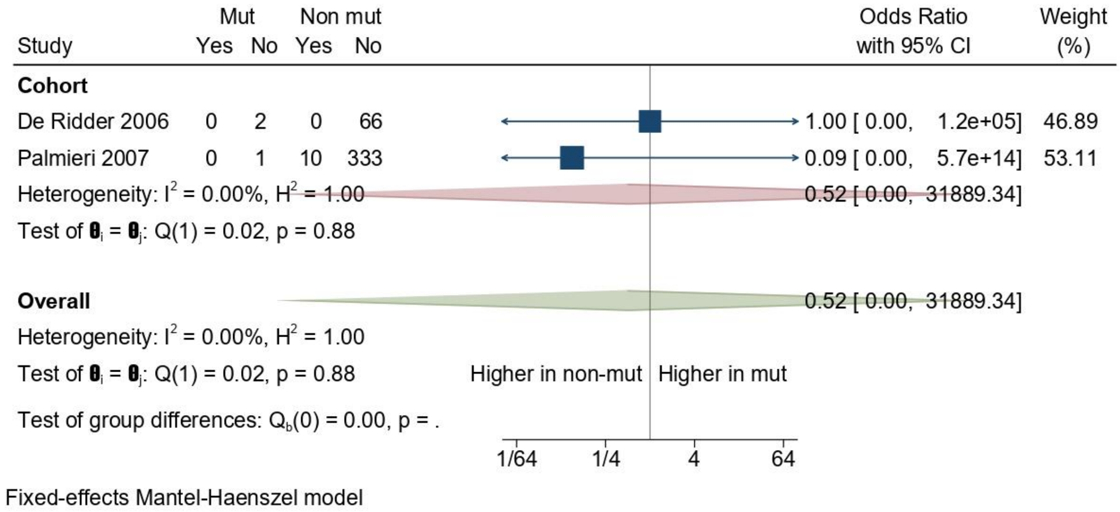


Figure S134. Forest plot of comparison *ITPA* 94C>A, 2 mutant alleles vs wild-type, outcome: Hepatotoxicity

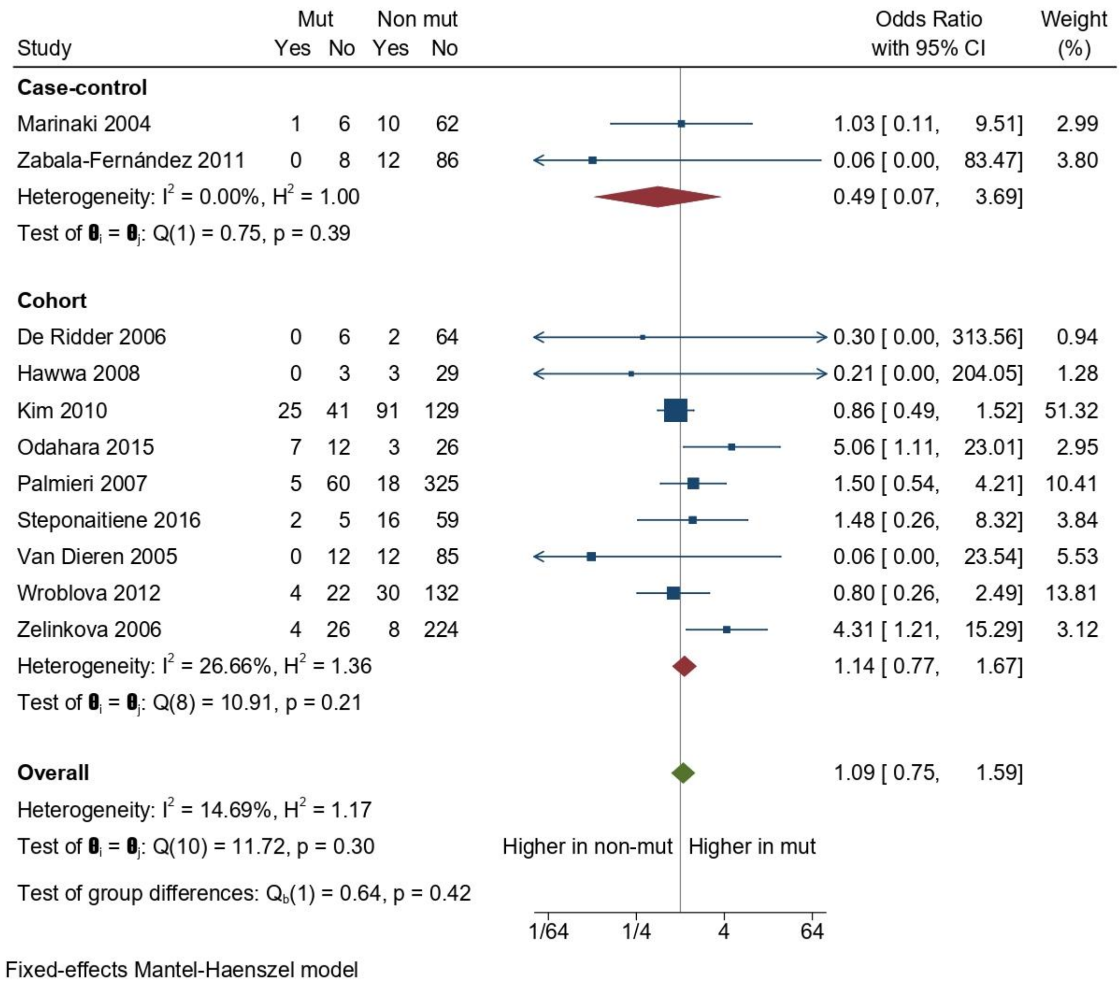


Figure S135. Forest plot of comparison mutated *ITPA* 94C>A vs wild-type, outcome: Total hematologic adverse events

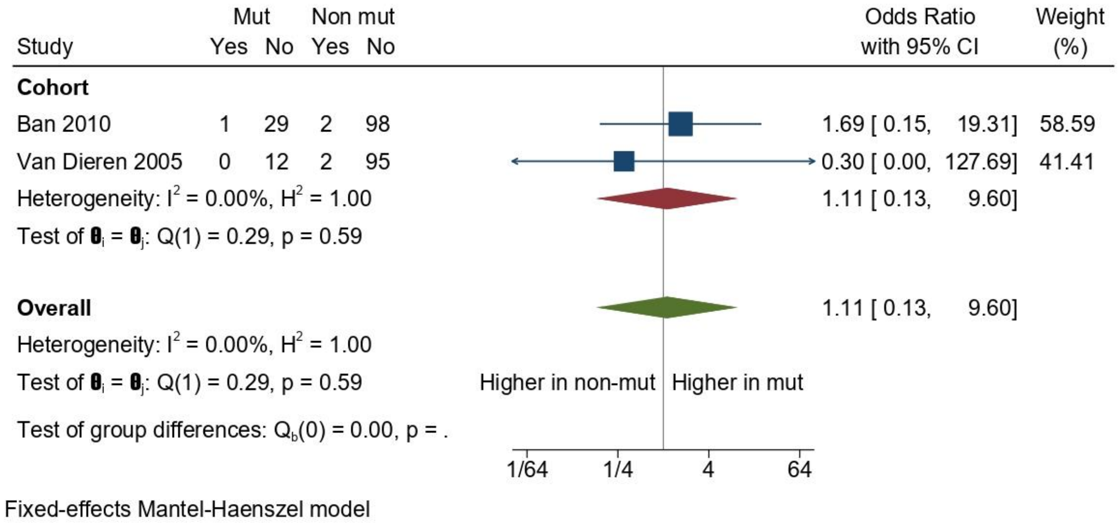


Figure S136. Forest plot of comparison mutated *ITPA* 94C>A vs wild-type, outcome: Serious hematologic adverse events

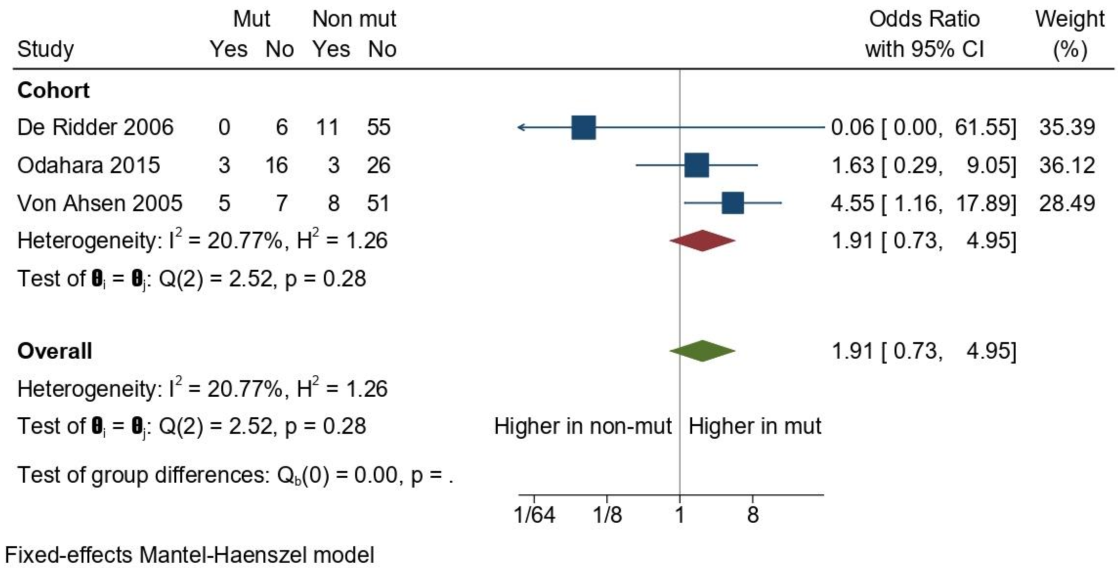


Figure S137. Forest plot of comparison mutated *ITPA* 94C>A vs wild-type, outcome: Withdrawal due to AE

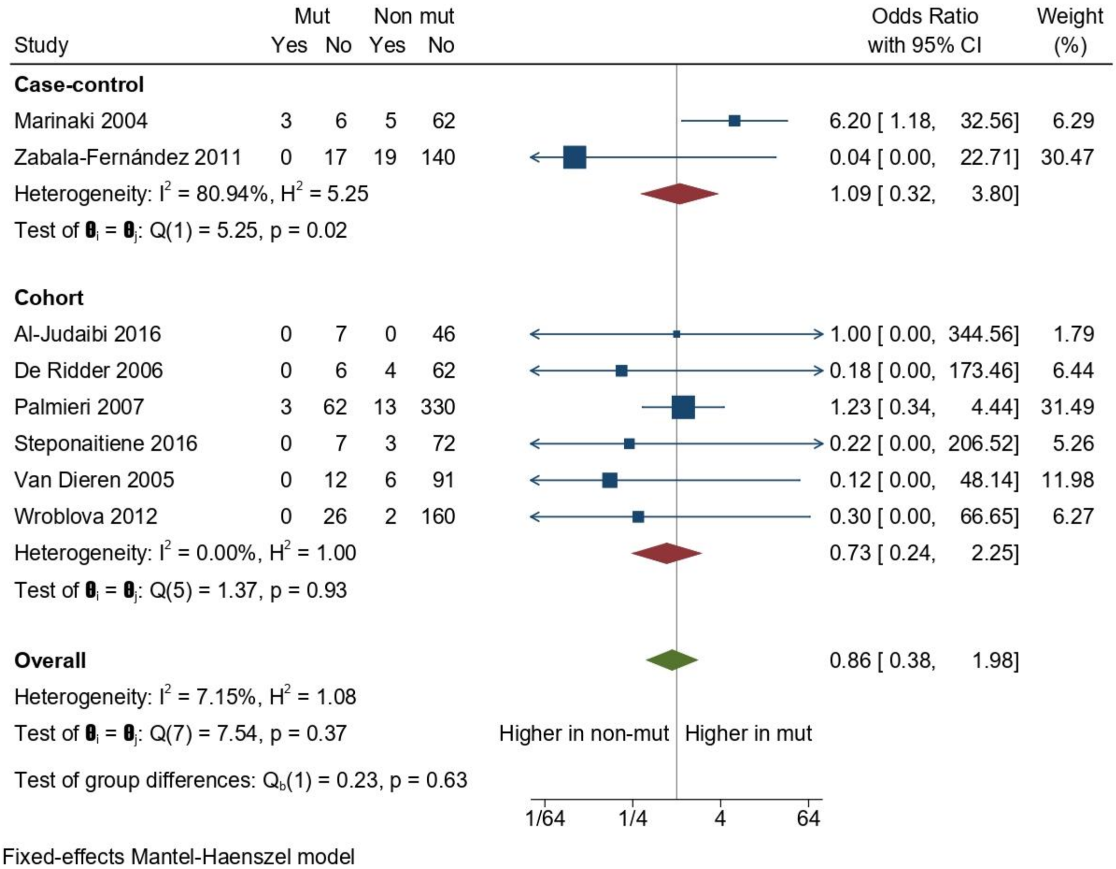


Figure S138. Forest plot of comparison mutated *ITPA* 94C>A vs wild-type, outcome: Pancreatitis

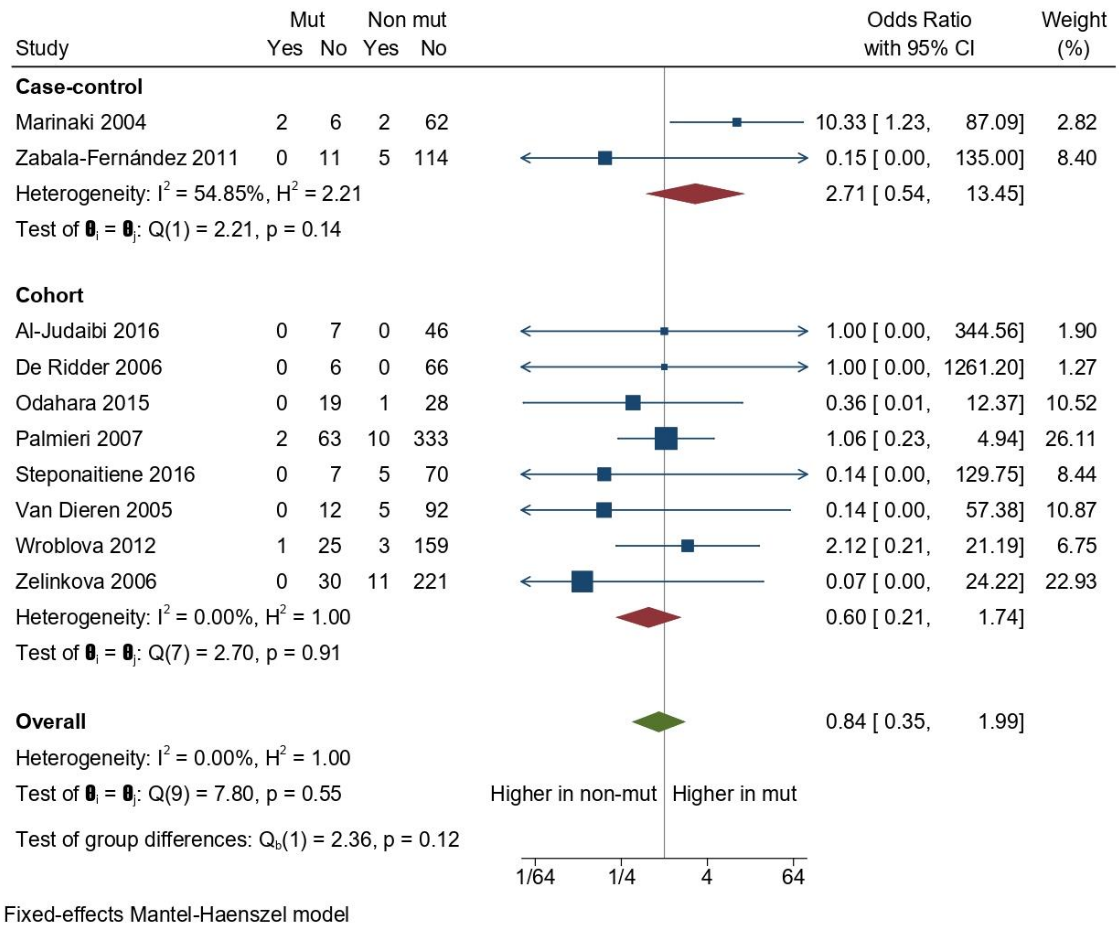


Figure S139. Forest plot of comparison mutated *ITPA* 94C>A vs wild-type, outcome: Hepatotoxicity

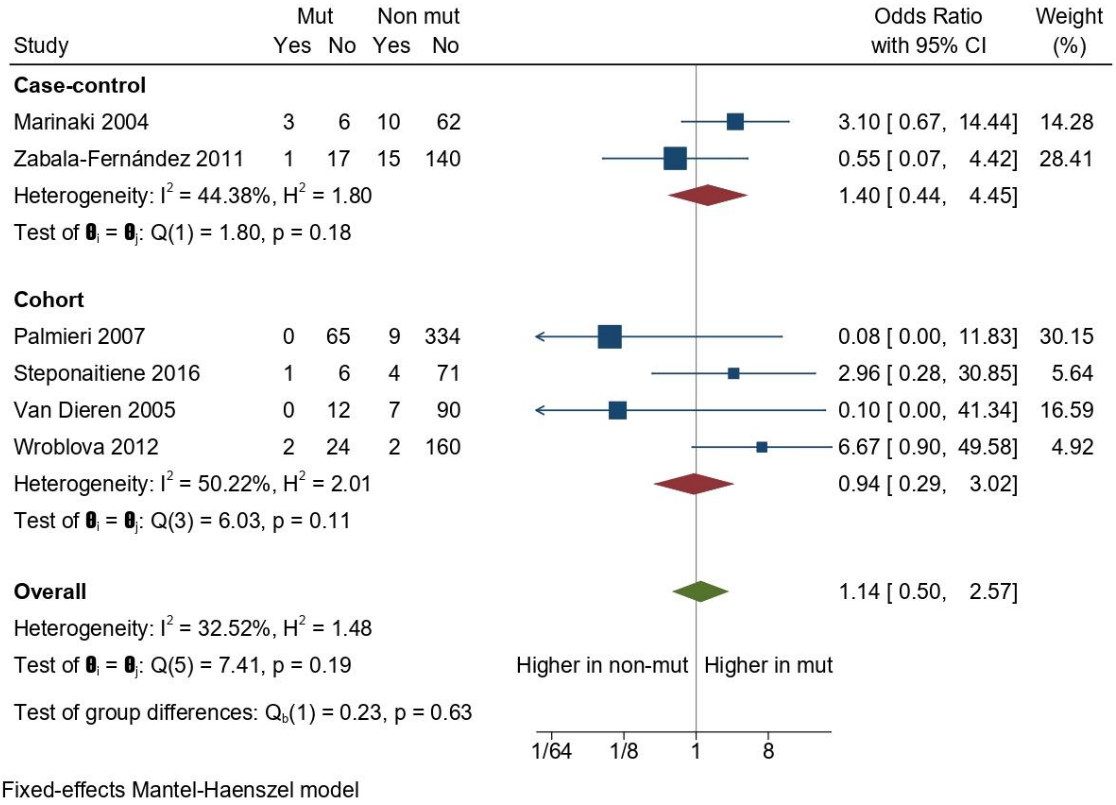


Figure S140. Forest plot of comparison mutated *ITPA* 94C>A vs wild-type, outcome: Gastrointestinal AE

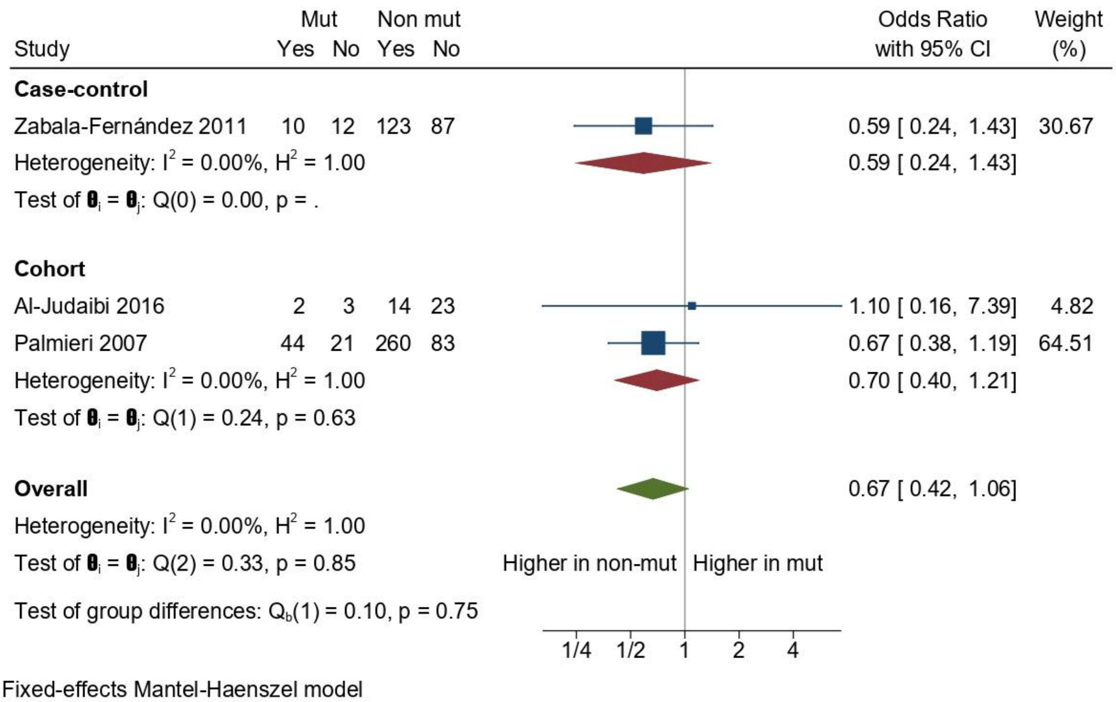


Figure S141. Forest plot of comparison mutated *ITPA* 94C>A vs wild-type, outcome: Clinical remission

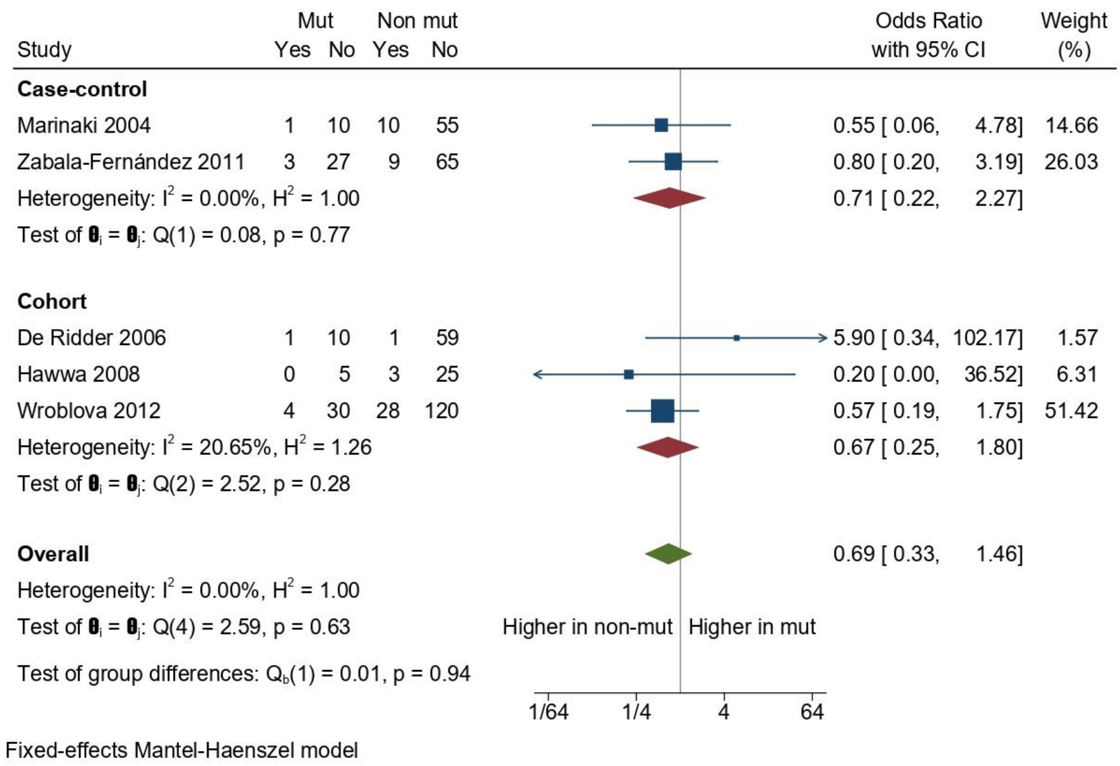


Figure S142. Forest plot of comparison *ITPA* IVS2 + 21A>C heterozygous vs wild-type, outcome: Total hematologic adverse events

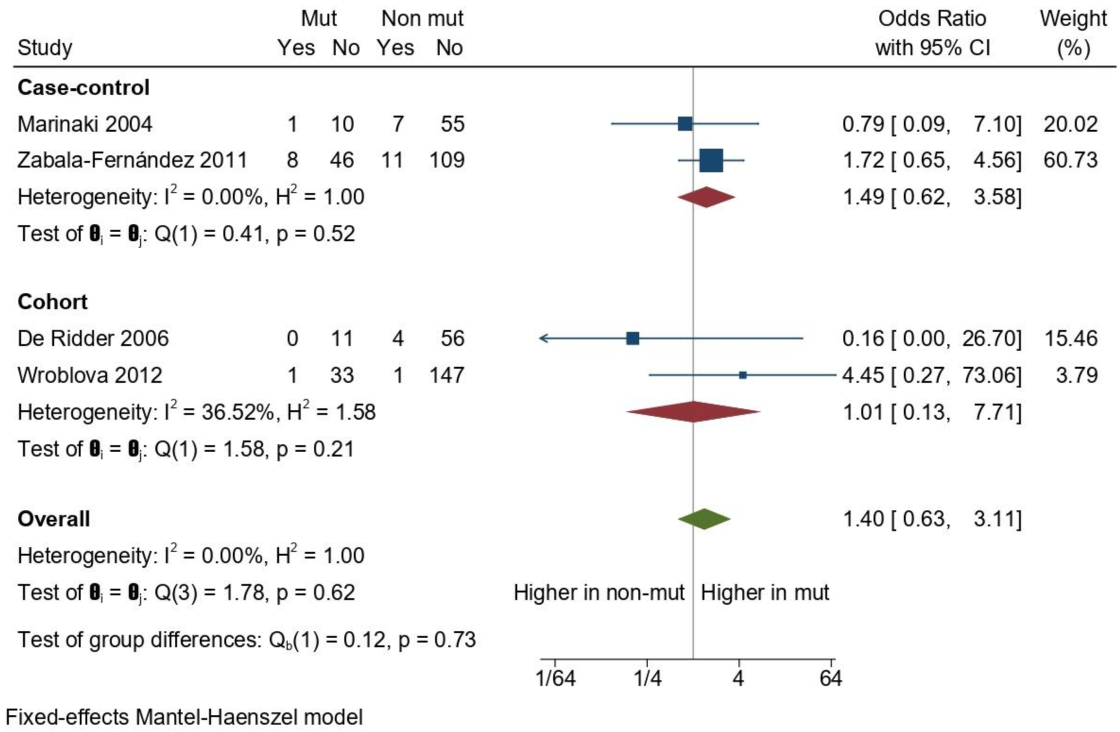


Figure S143. Forest plot of comparison *ITPA* IVS2 + 21A>C heterozygous vs wild-type, outcome: Pancreatitis

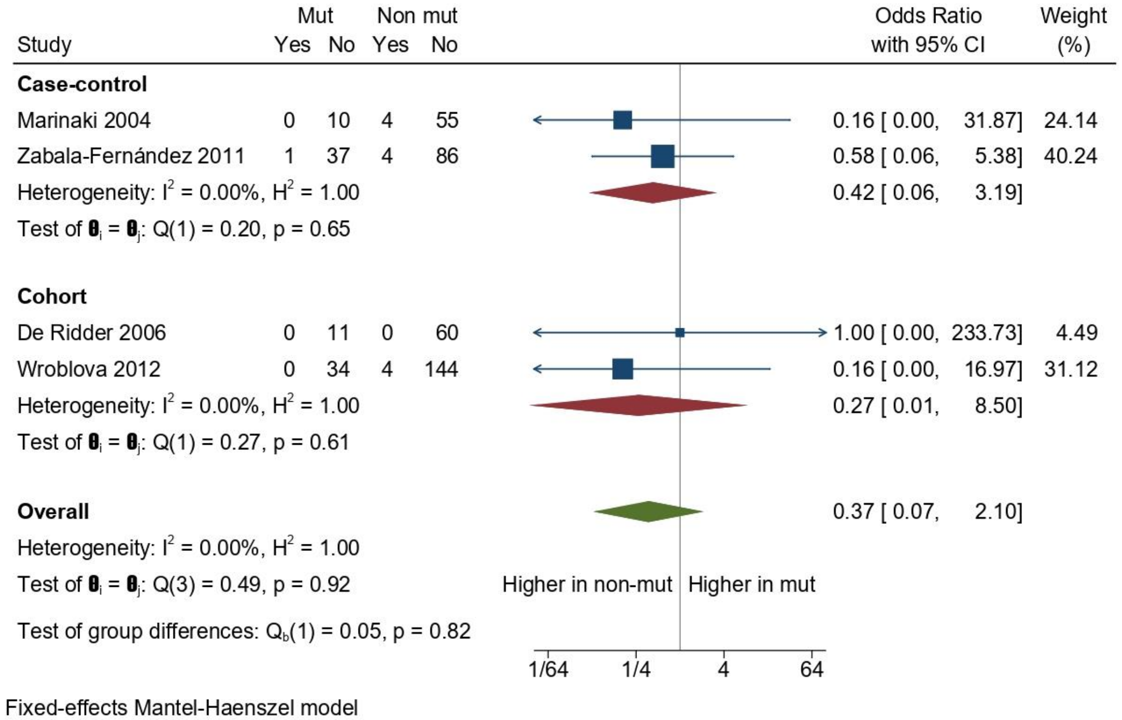


Figure S144. Forest plot of comparison *ITPA* IVS2 + 21A>C heterozygous vs wild-type, outcome: Hepatotoxicity

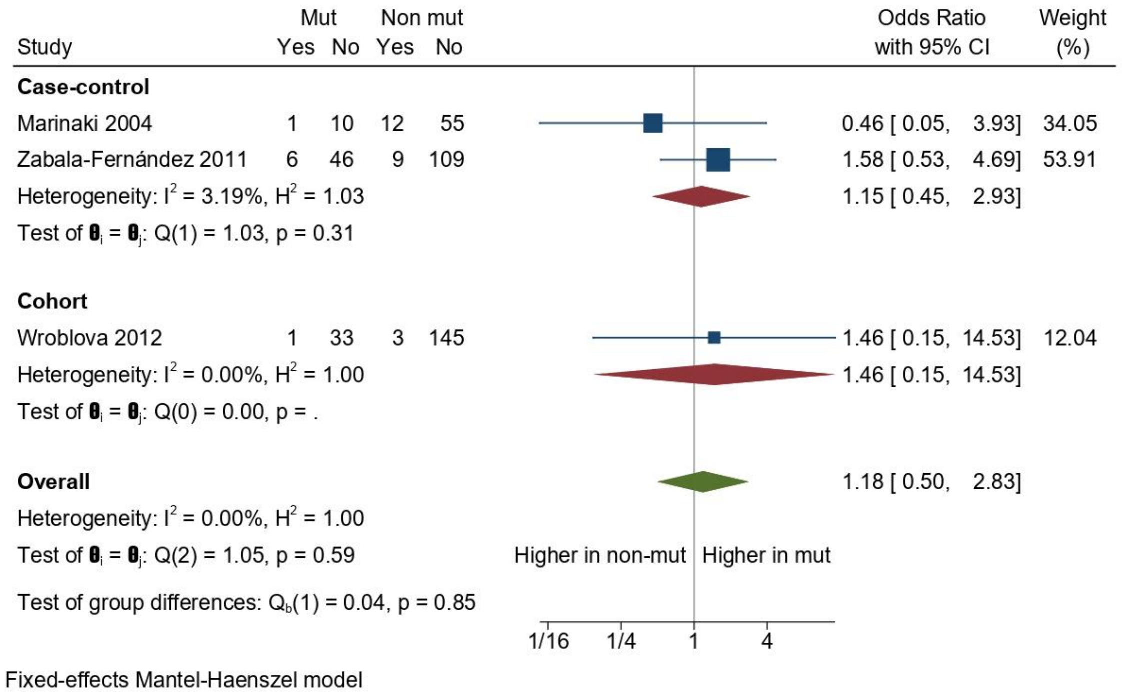


Figure S145. Forest plot of comparison *ITPA* IVS2 + 21A>C heterozygous vs wild-type, outcome: Gastrointestinal side effects

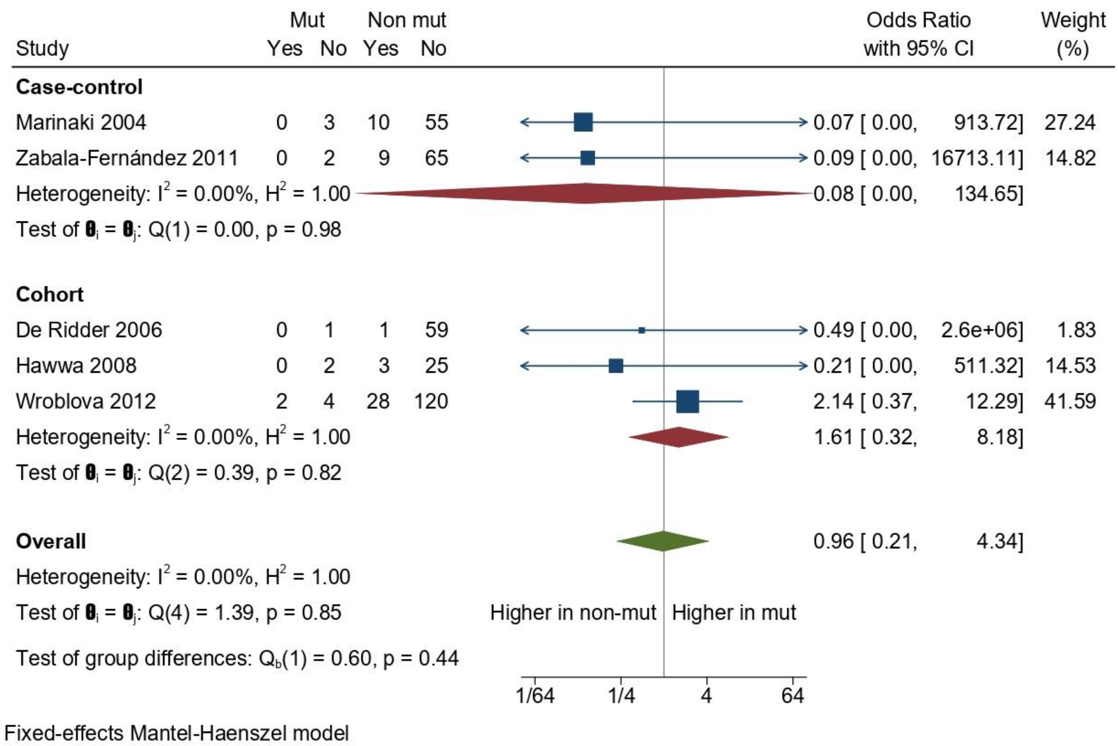


Figure S146. Forest plot of comparison *ITPA* IVS2 + 21A>C, 2 mutant alleles vs wild-type, outcome: Total hematologic adverse events

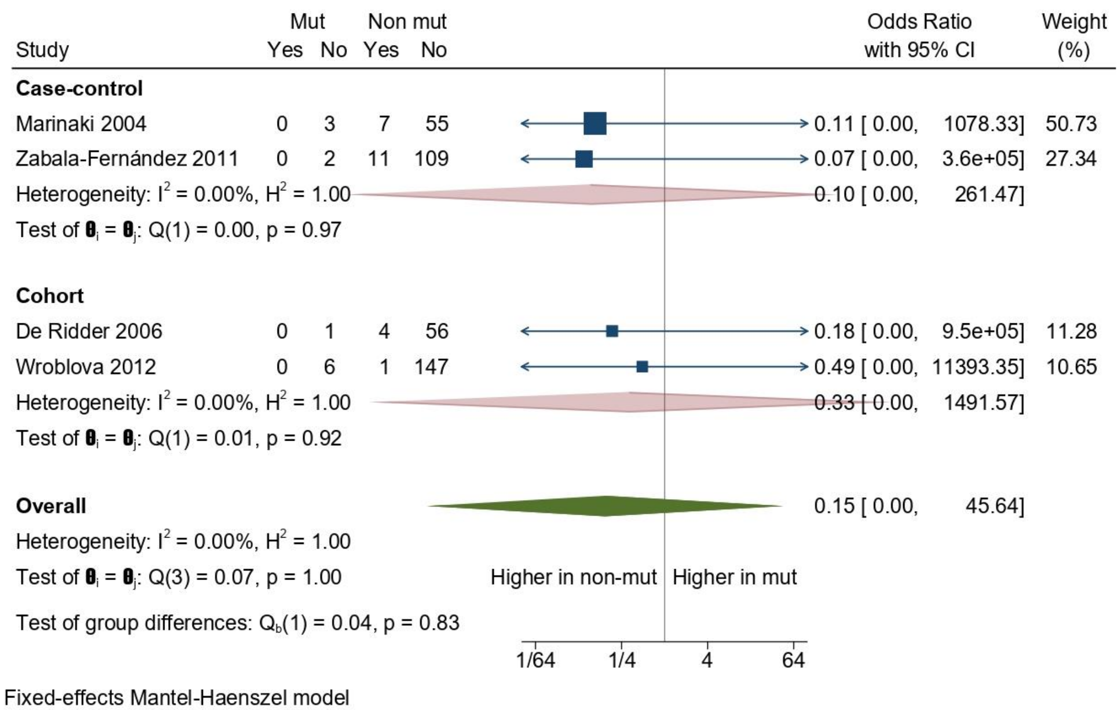


Figure S147. Forest plot of comparison *ITPA* IVS2 + 21A>C, 2 mutant alleles vs wild-type, outcome: Pancreatitis

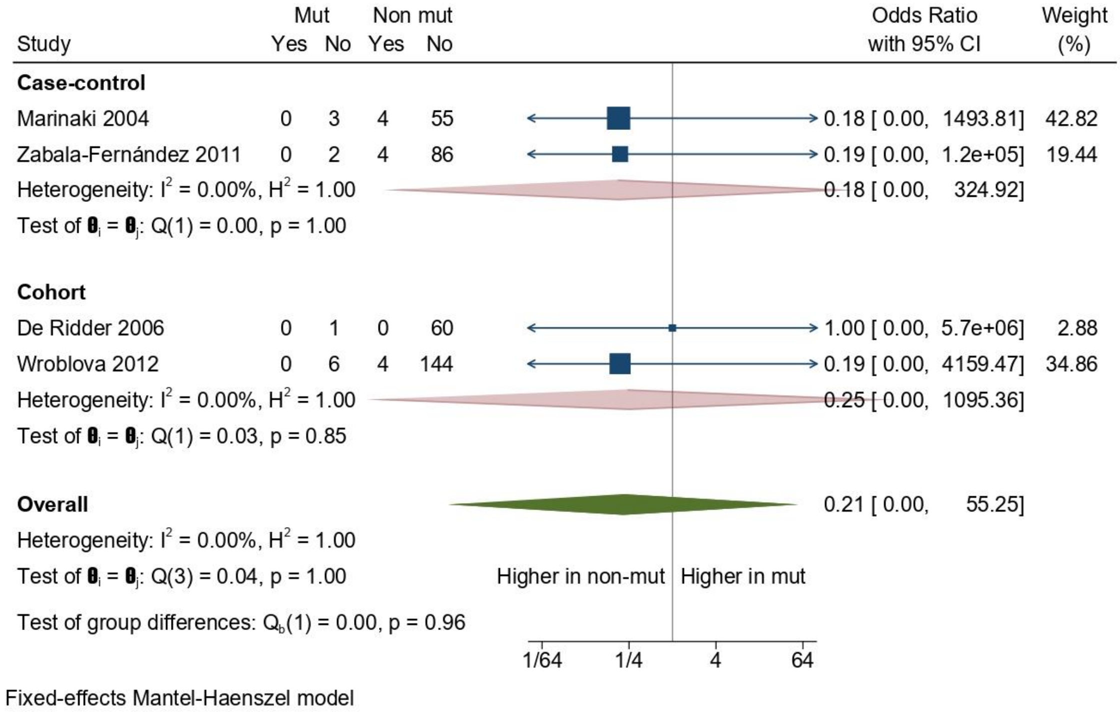


Figure S148. Forest plot of comparison *ITPA* IVS2 + 21A>C, 2 mutant alleles vs wild-type, outcome: Hepatotoxicity

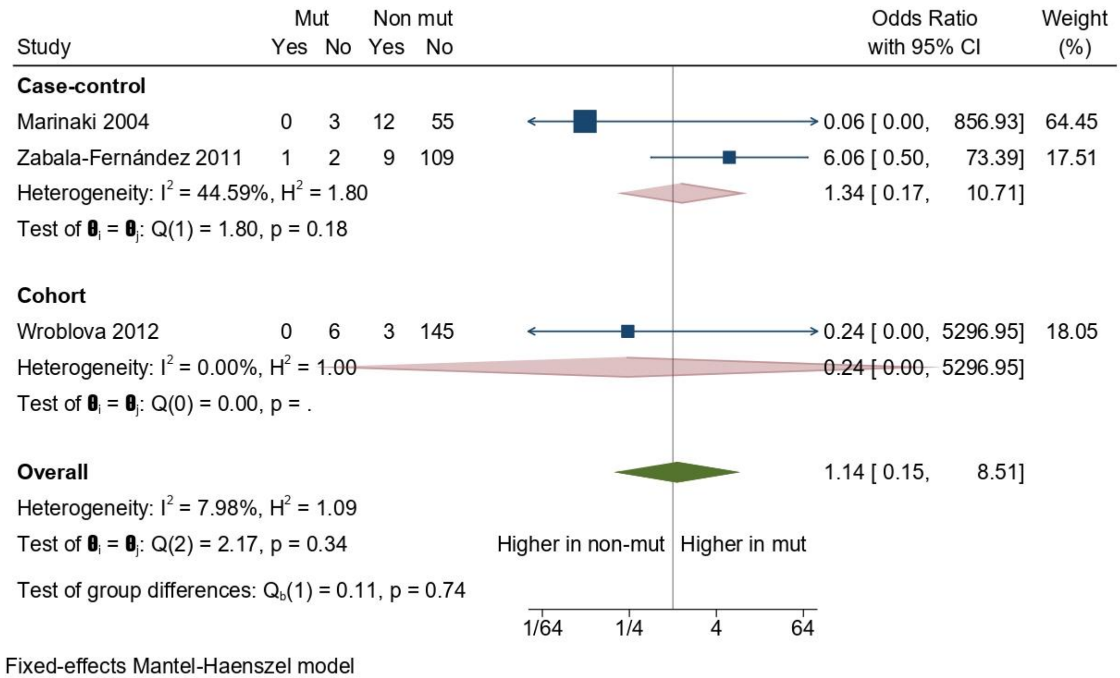


Figure S149. Forest plot of comparison *ITPA* IVS2 + 21A>C, 2 mutant alleles vs wild-type, outcome: Gastrointestinal side effects

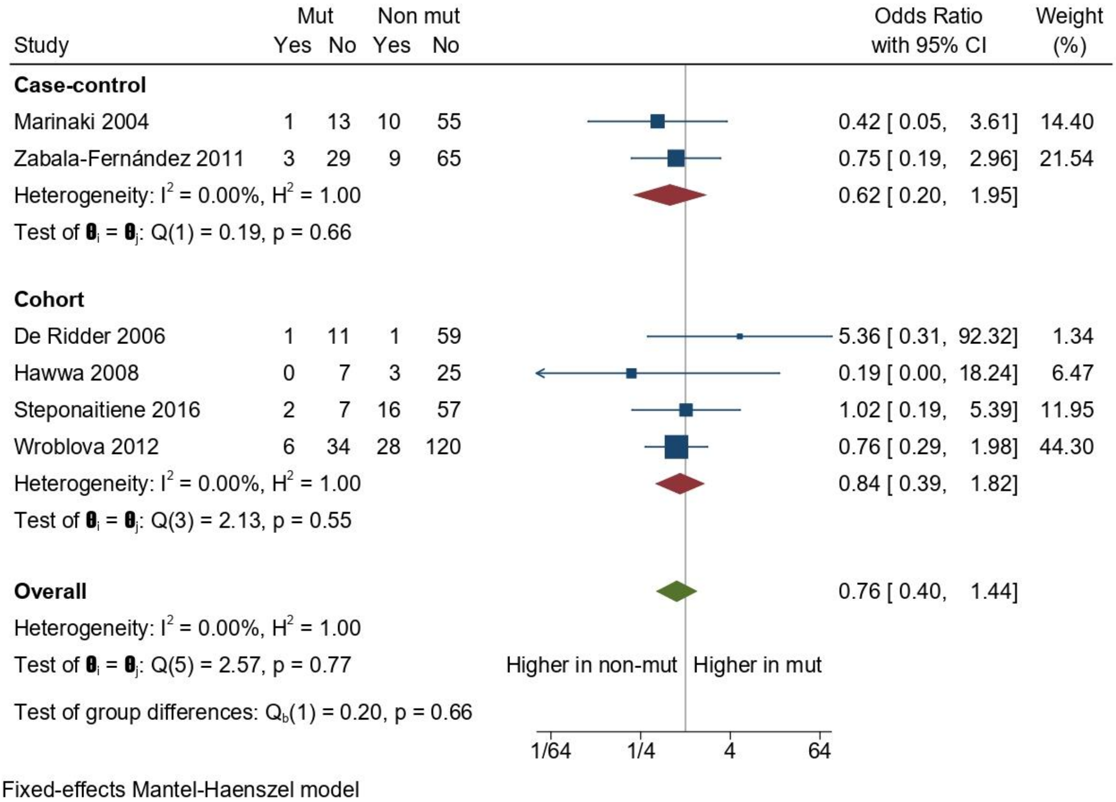


Figure S150. Forest plot of comparison mutated *ITPA* IVS2 + 21A>C vs wild-type, outcome: Total hematologic adverse events

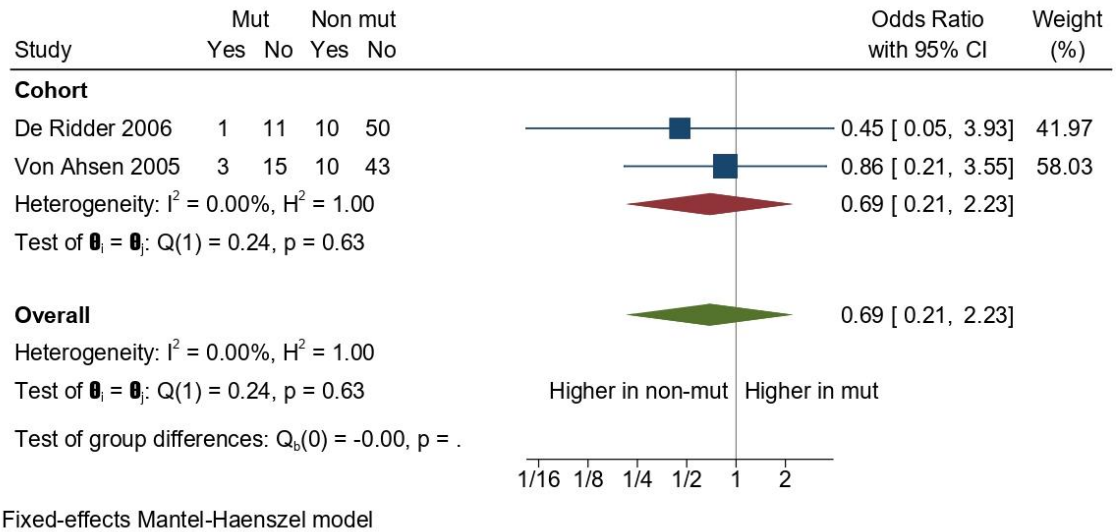


Figure S151. Forest plot of comparison mutated *ITPA* IVS2 + 21A>C vs wild-type, outcome: Withdrawal due to AE

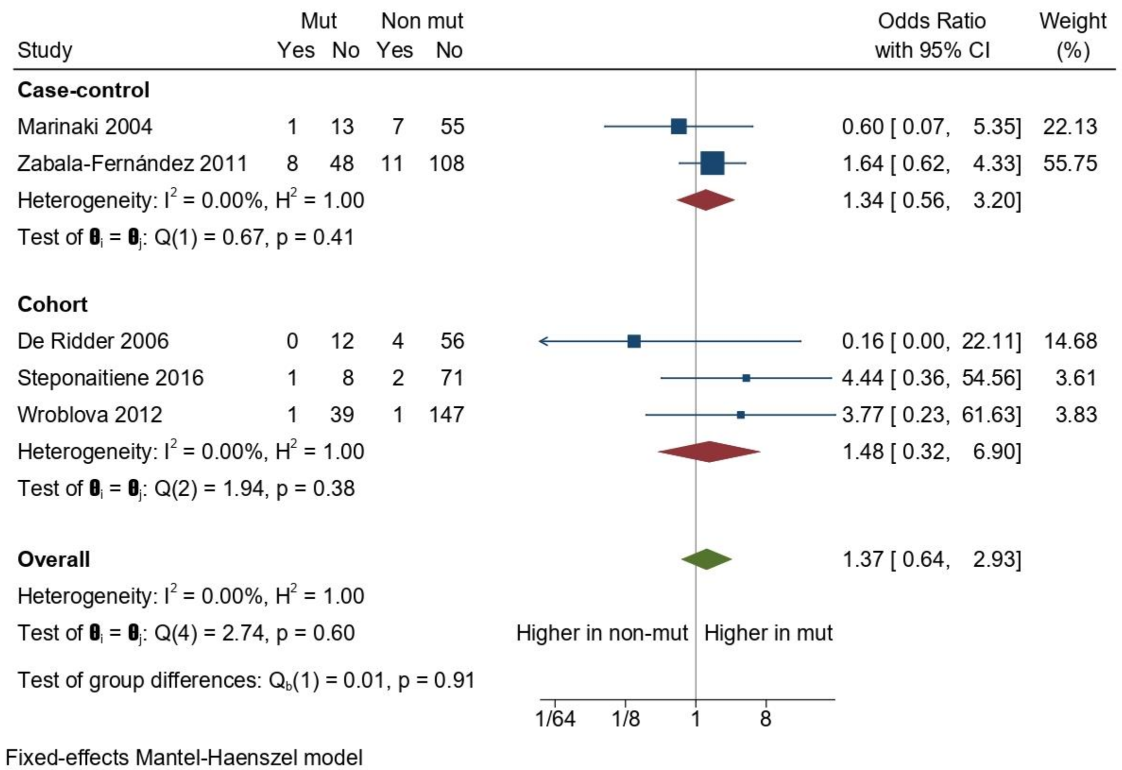


Figure S152. Forest plot of comparison mutated *ITPA* IVS2 + 21A>C vs wild-type, outcome: Pancreatitis

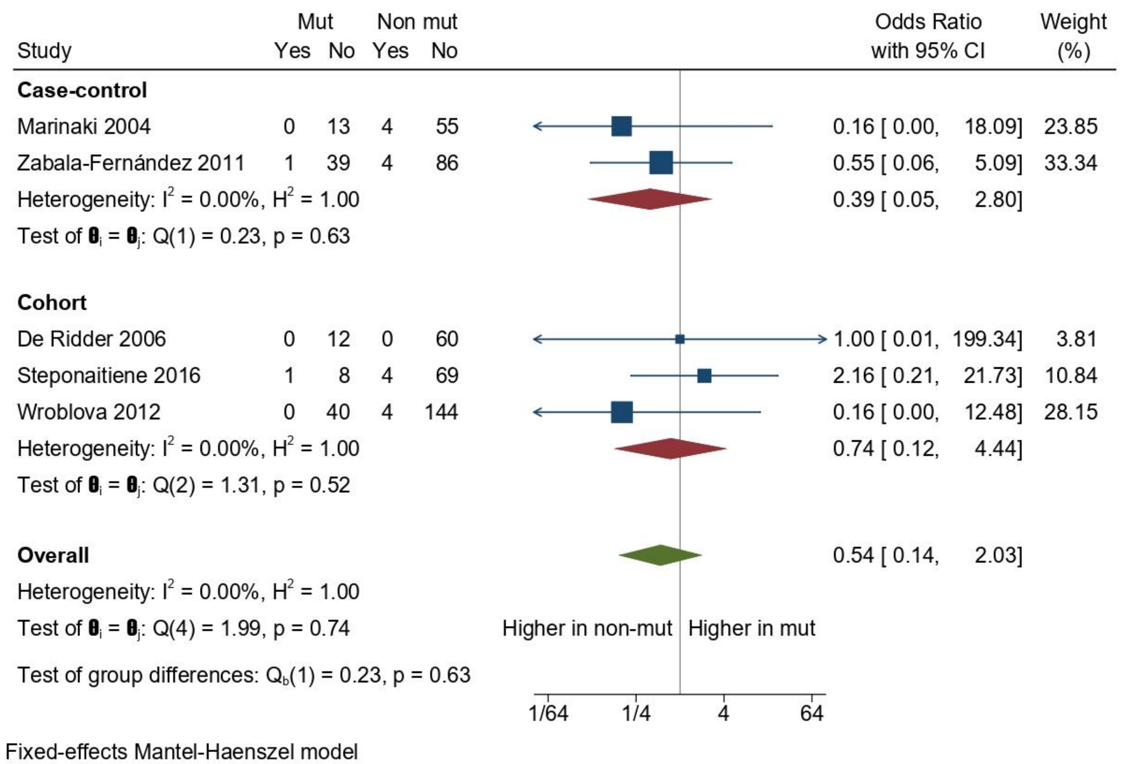


Figure S153. Forest plot of comparison mutated *ITPA* IVS2 + 21A>C vs wild-type, outcome: Hepatotoxicity

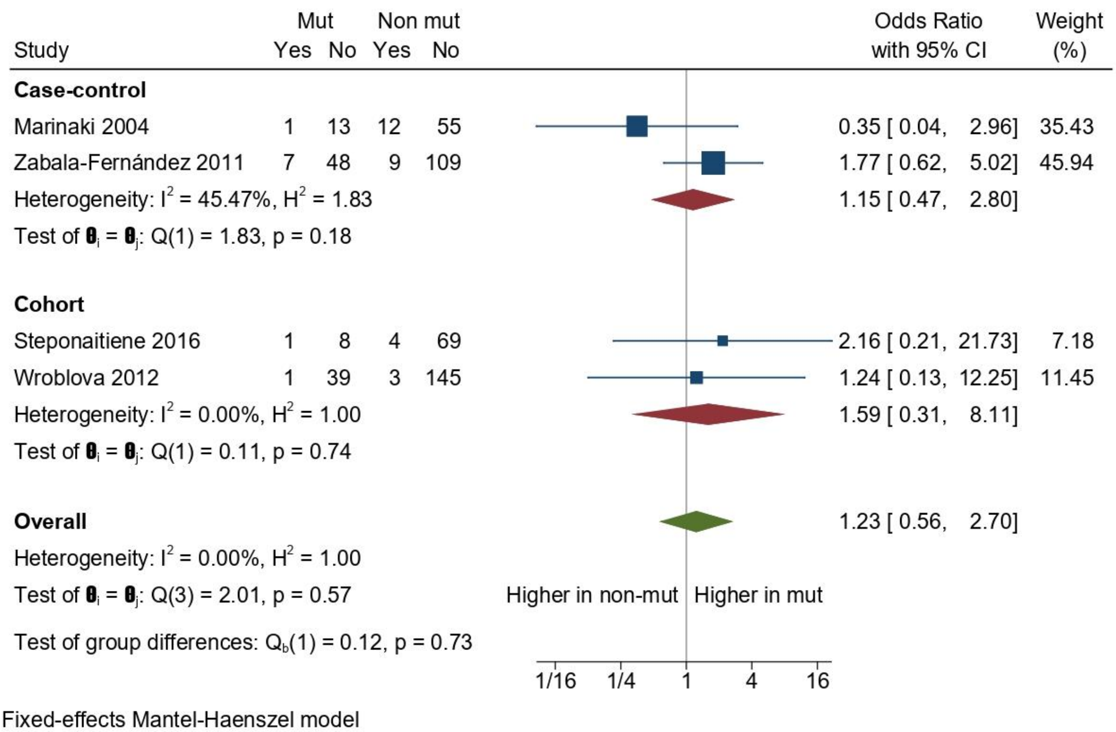


Figure S154. Forest plot of comparison mutated *ITPA* IVS2 + 21A>C vs wild-type, outcome: Gastrointestinal side effects

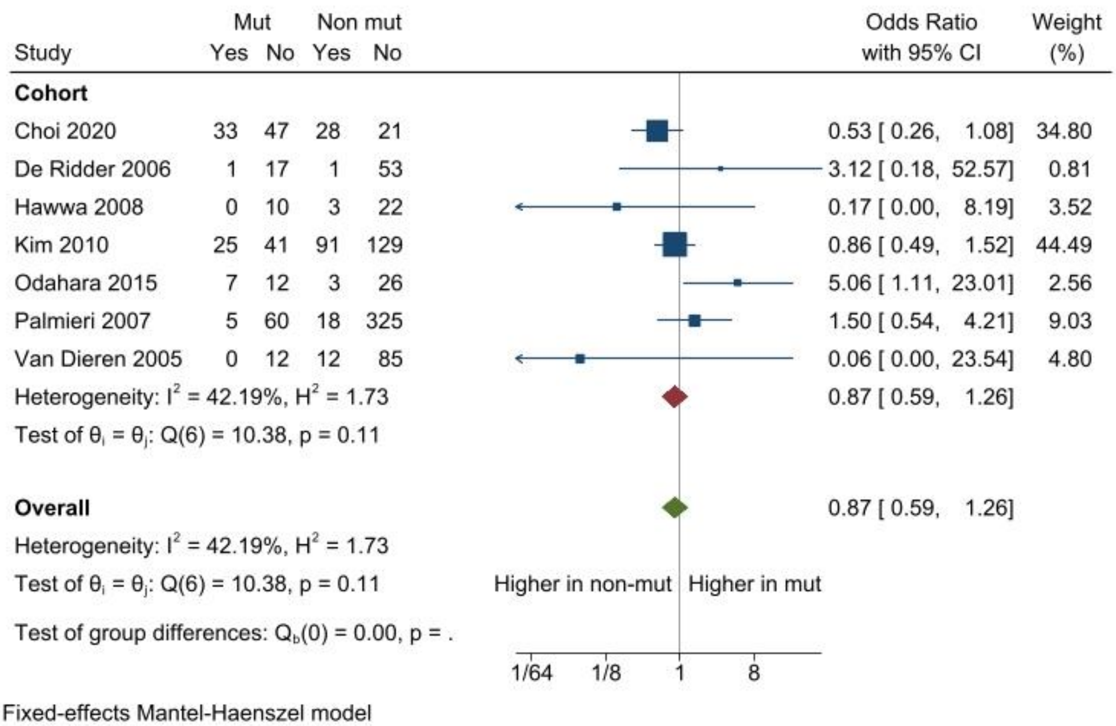


Figure S155. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *ITPA* vs wild-type, outcome: Total hematologic AE

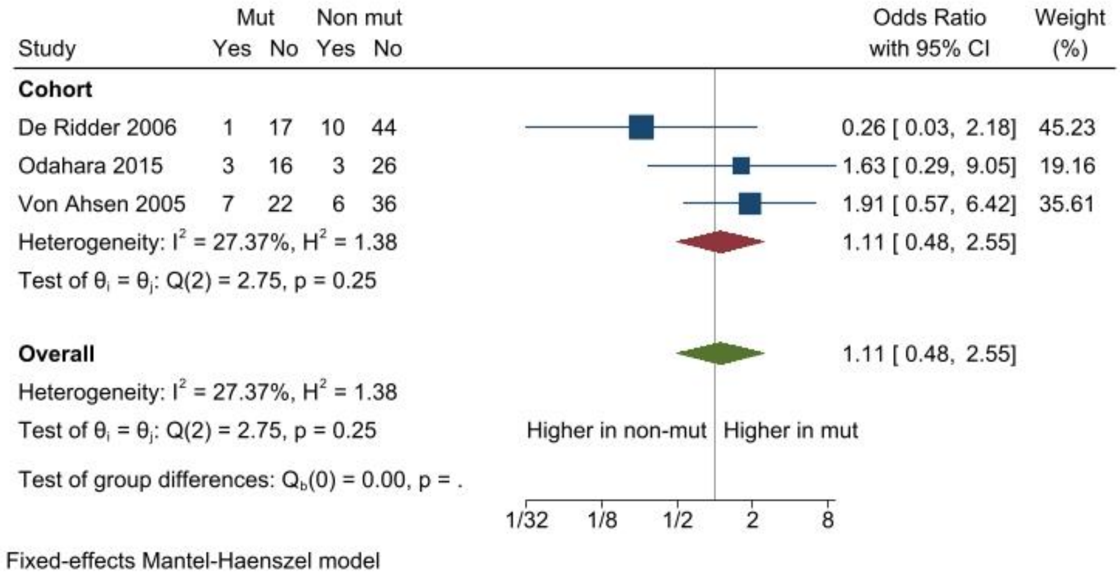


Figure S156. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *ITPA* vs wild-type, outcome: Withdrawal due to AE

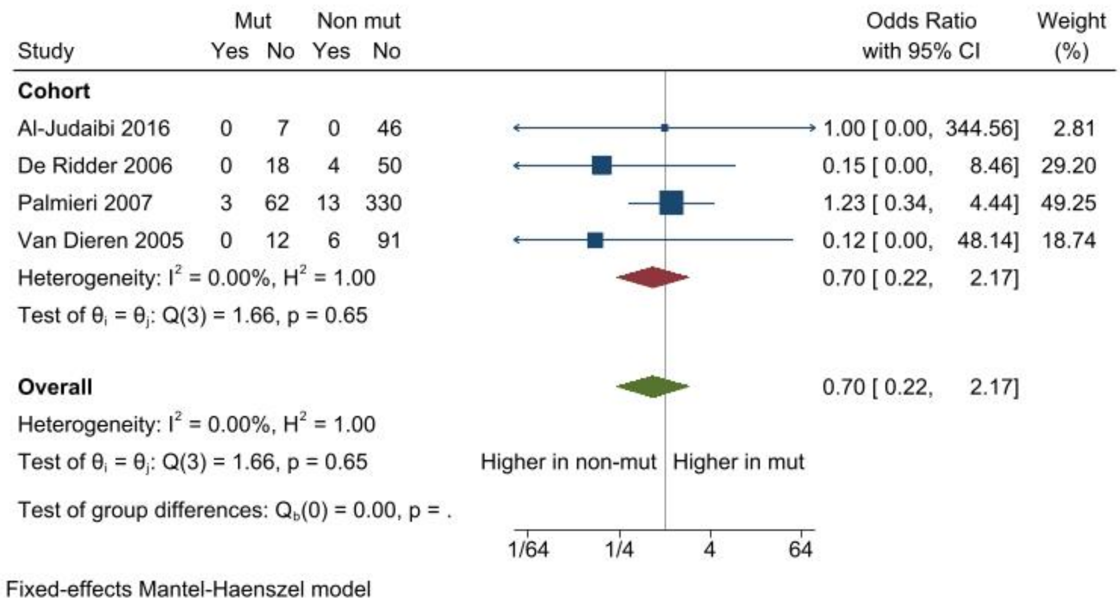


Figure S157. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *ITPA* vs wild-type, outcome: Pancreatitis

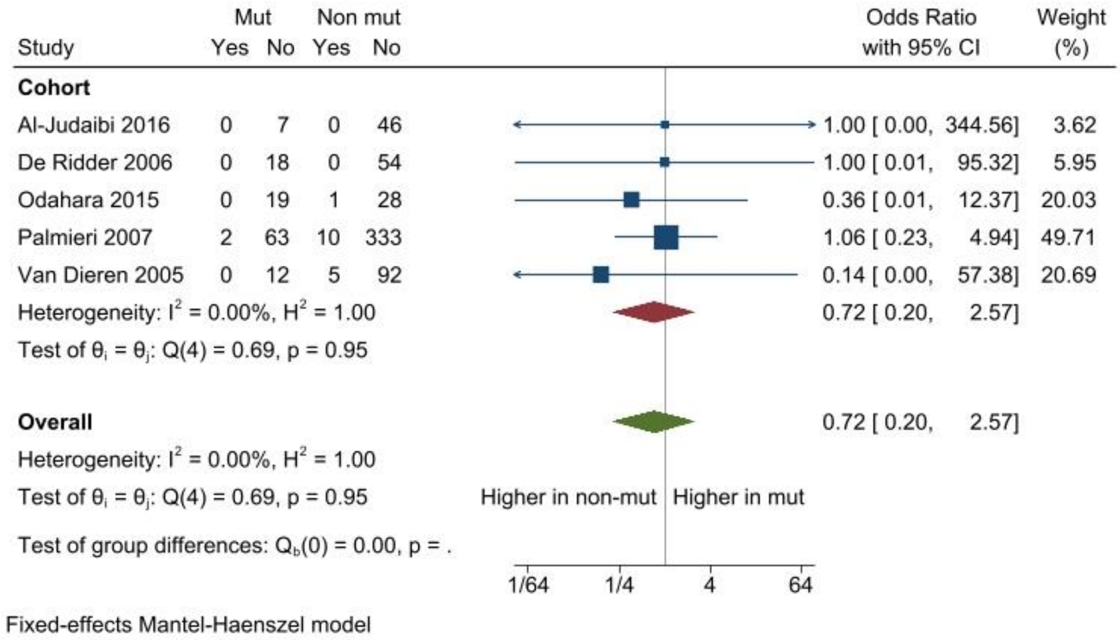


Figure S158. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *ITPA* vs wild-type, outcome: Hepatotoxicity

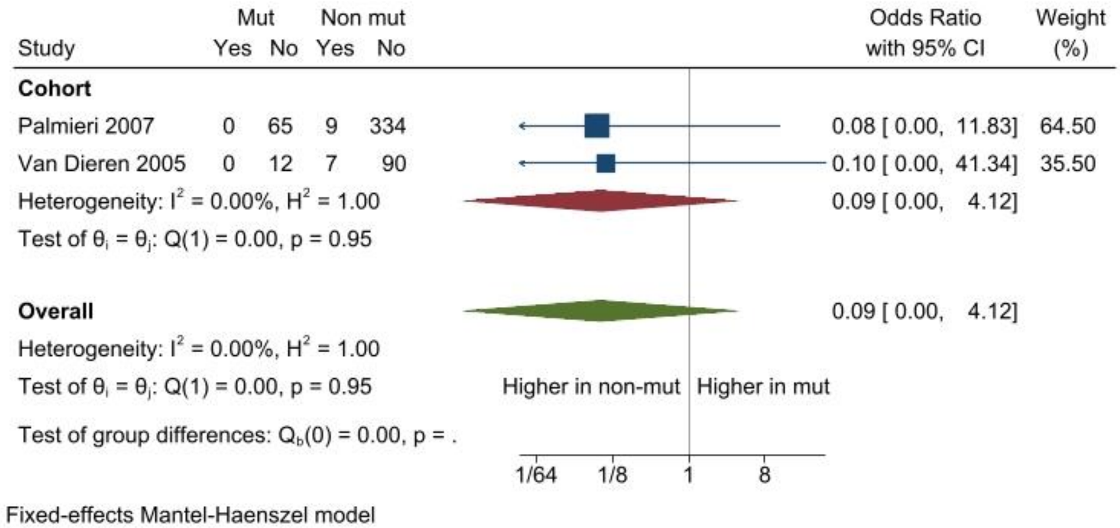


Figure S159. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *ITPA* vs wild-type, outcome: Gastrointestinal side effects

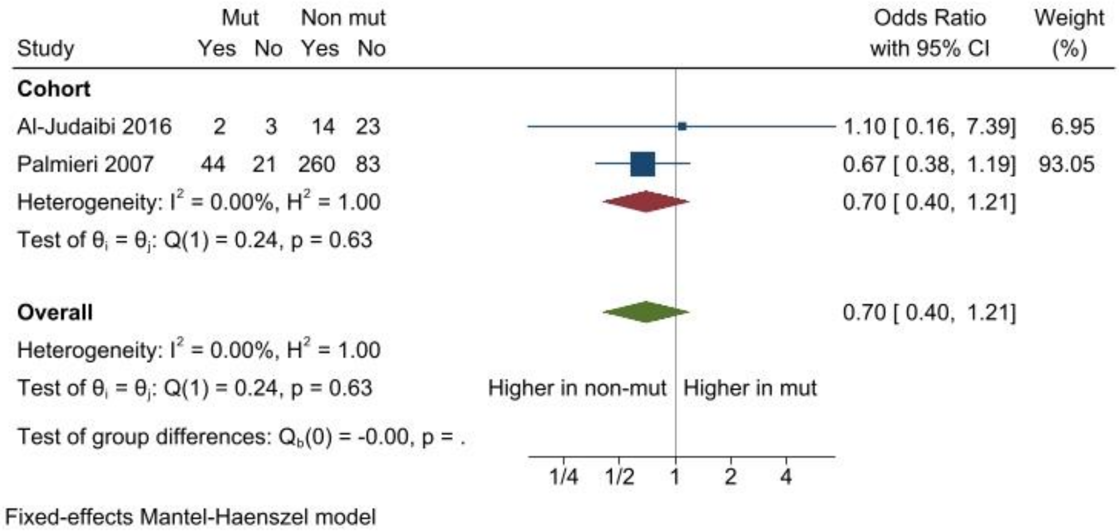


Figure S160. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *ITPA* vs wild-type, outcome: Clinical remission

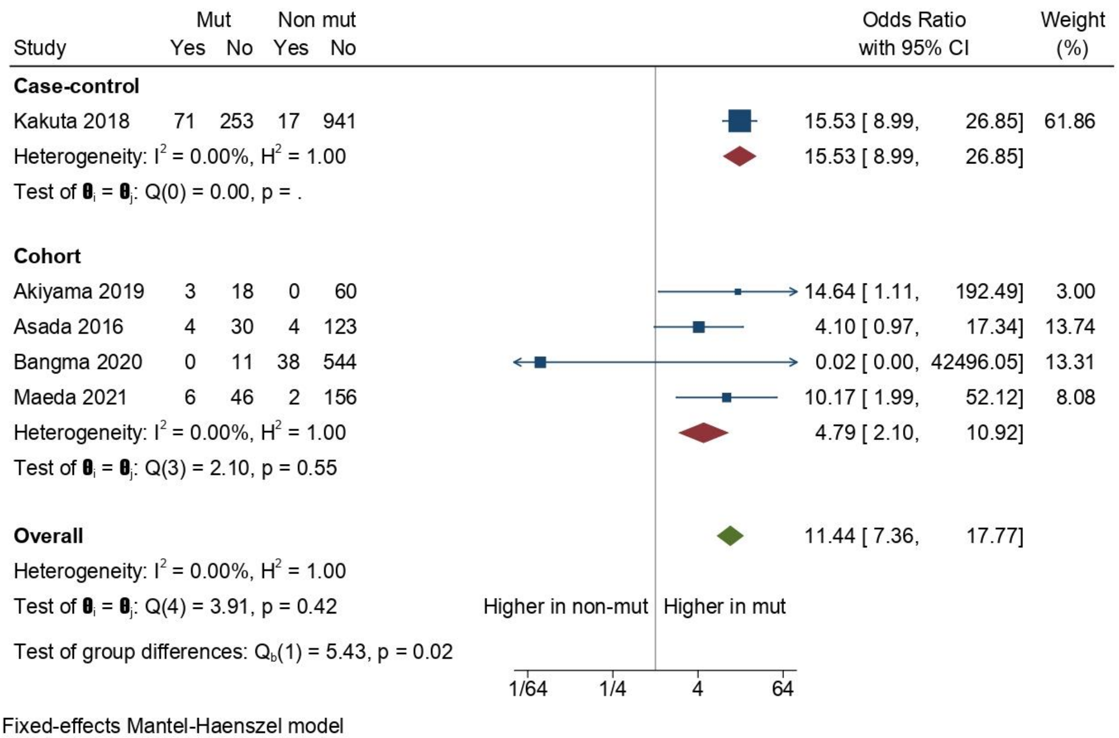


Figure S161. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Total serious adverse events

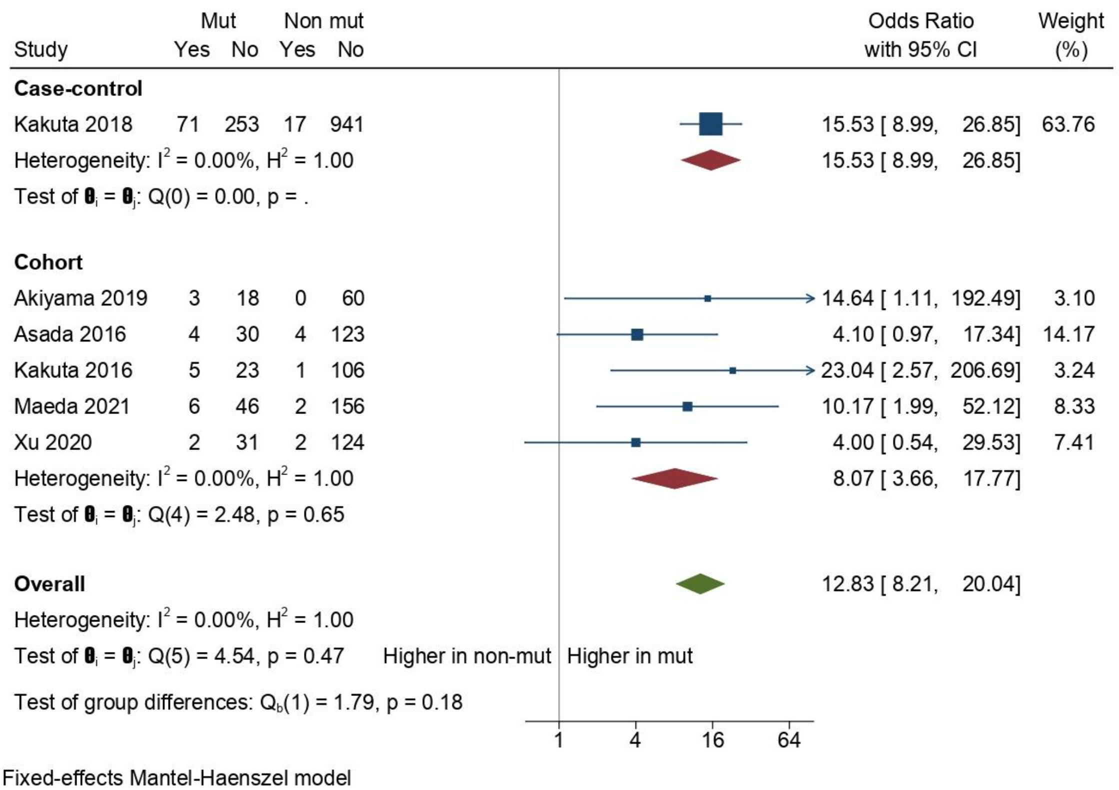


Figure S162. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Serious hematologic adverse events

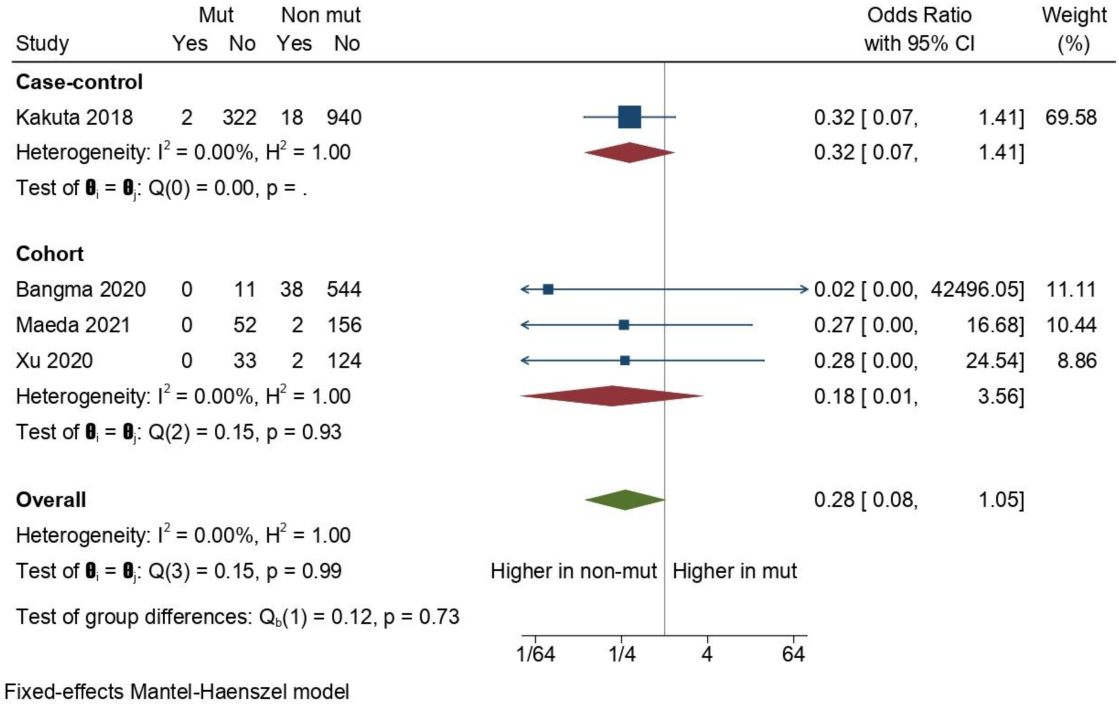


Figure S163. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Pancreatitis

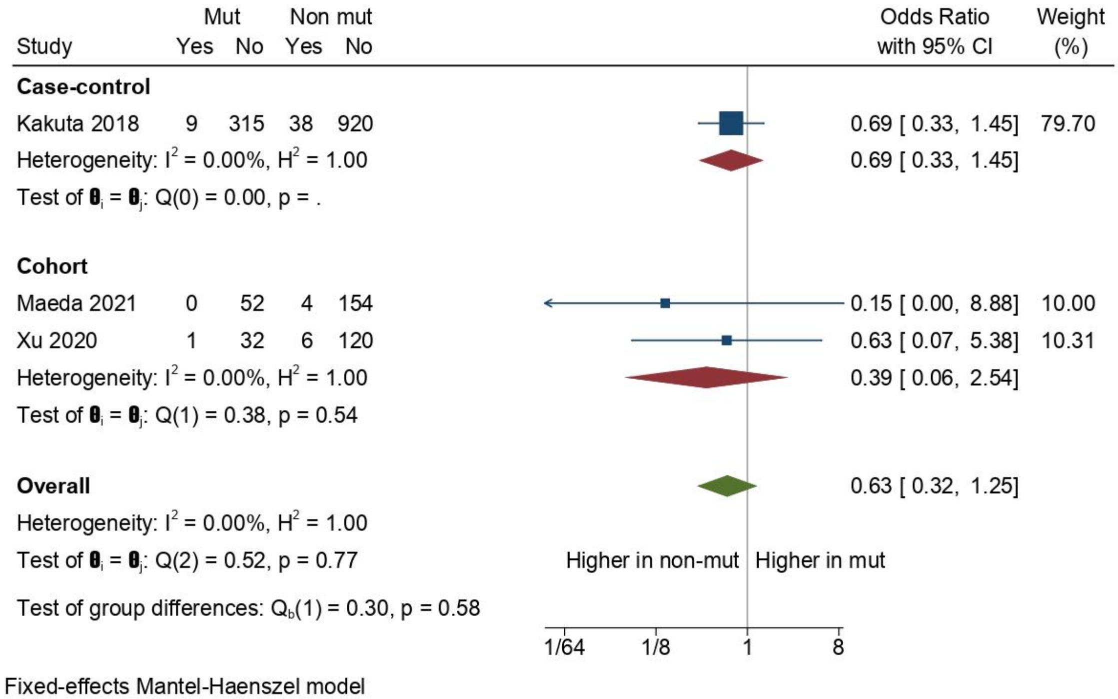


Figure S164. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Hepatotoxicity

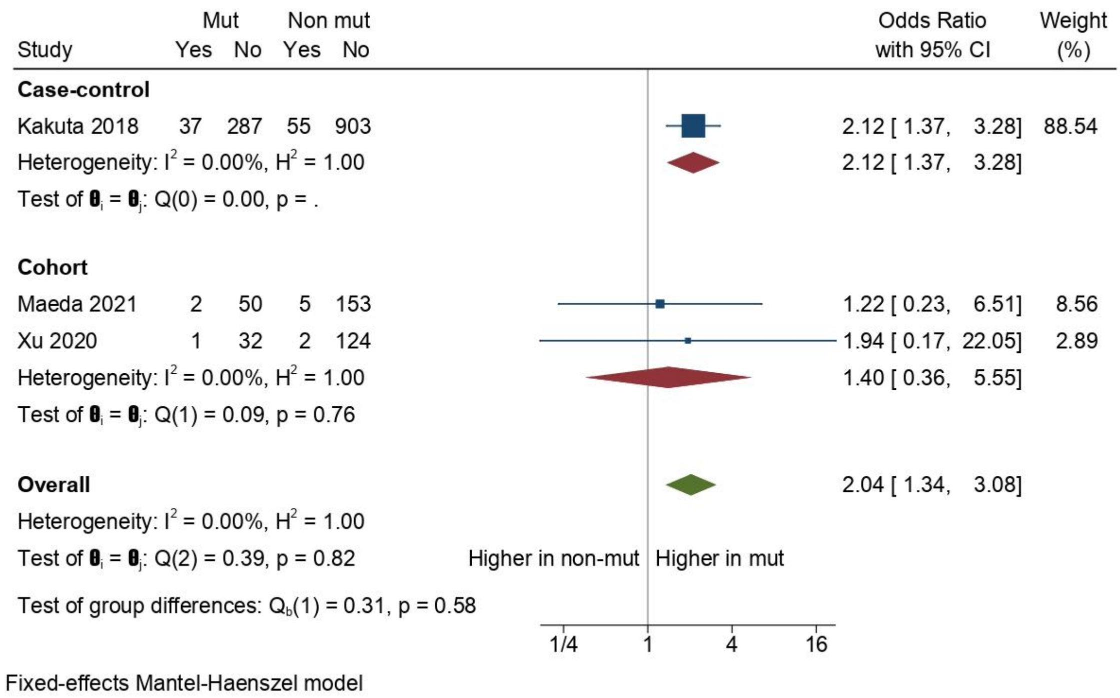
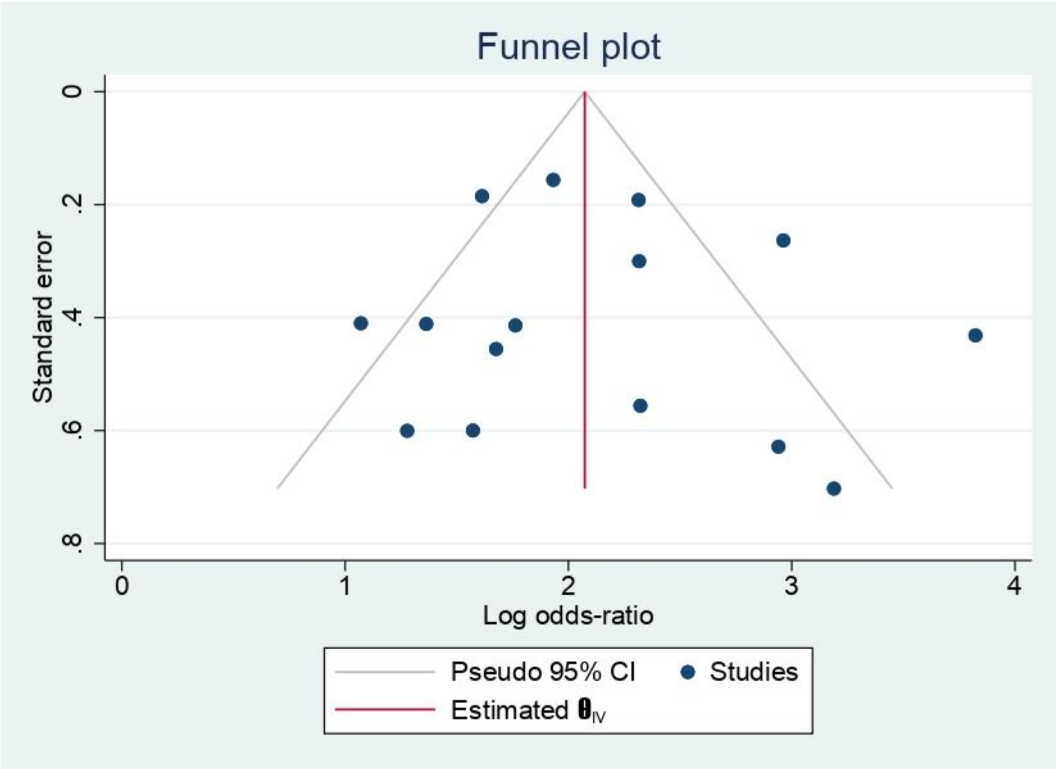


Figure S165. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Gastrointestinal side effects



Test for Funnel Plot Asymmetry: z = -4.28, p < 0.001

Figure S166. Funnel plot of comparison mutated *NUDT15* vs wild-type *NUDT15*, outcome: Total hematologic adverse events

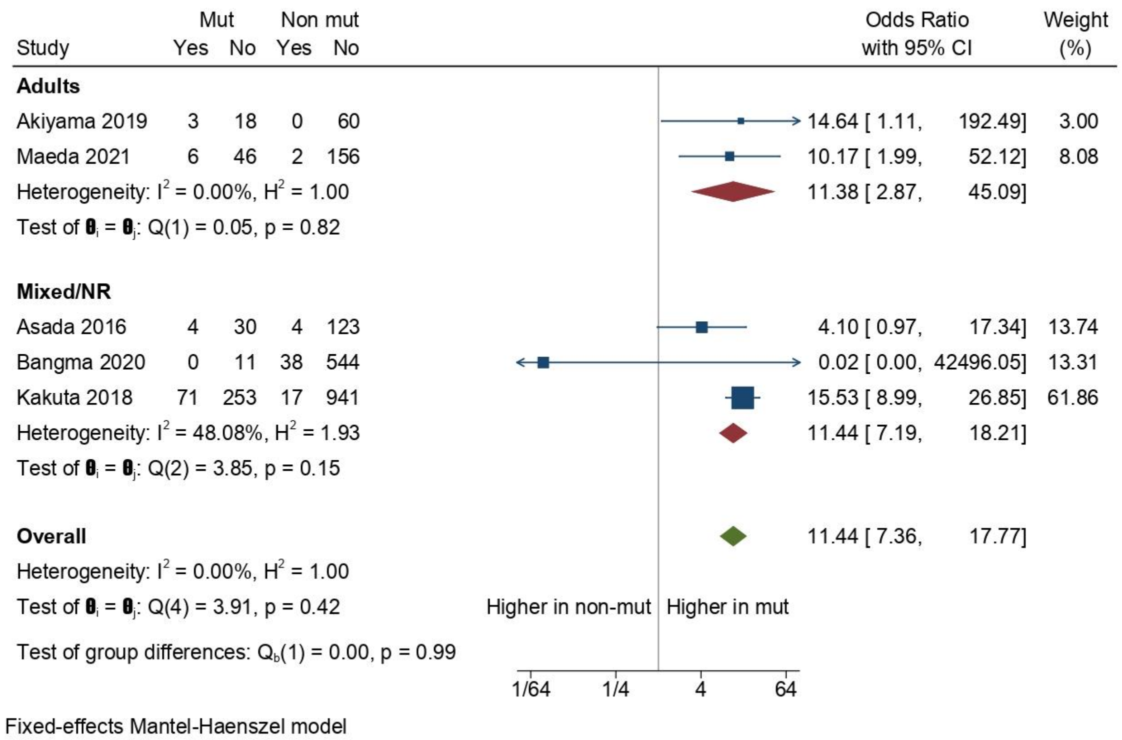


Figure S167. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Total serious adverse events. Subgroup analysis according to age

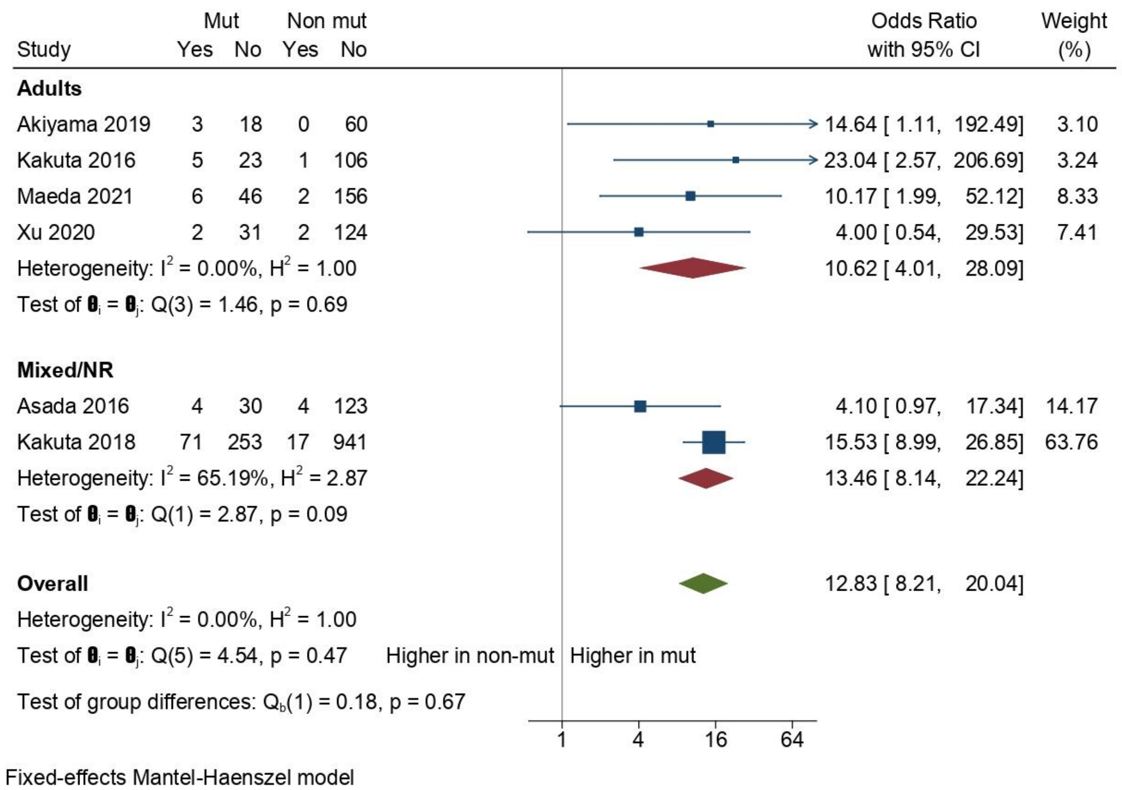


Figure S168. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Serious hematologic adverse events. Subgroup analysis according to age

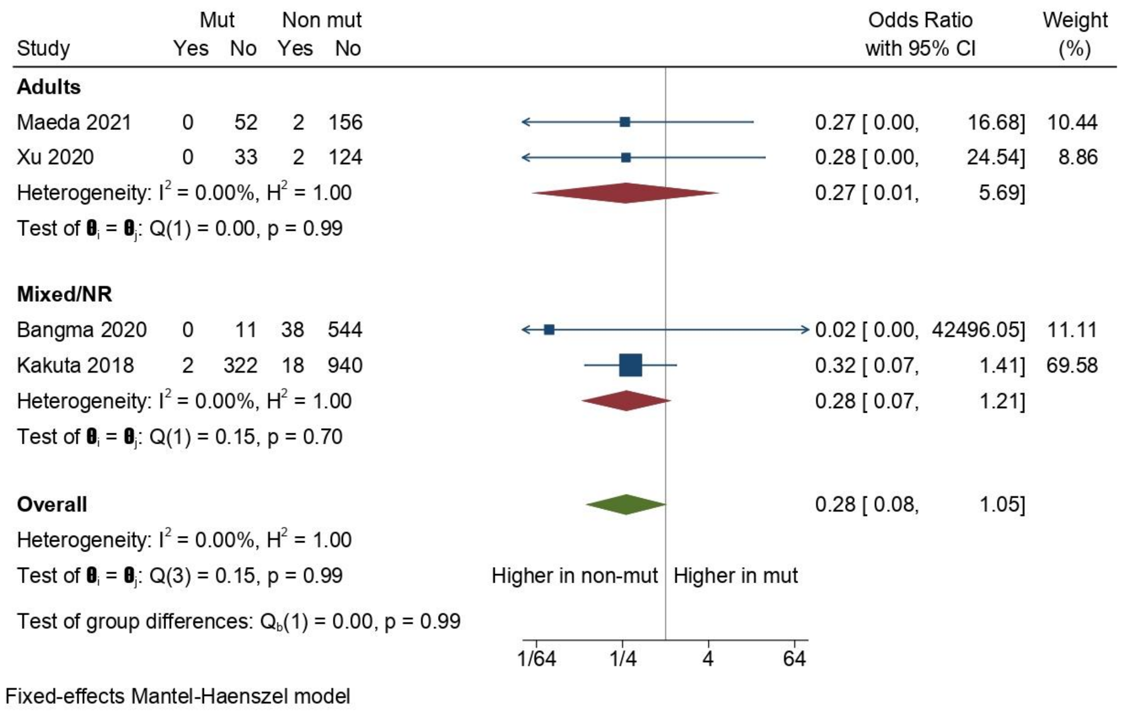


Figure S169. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Pancreatitis. Subgroup analysis according to age

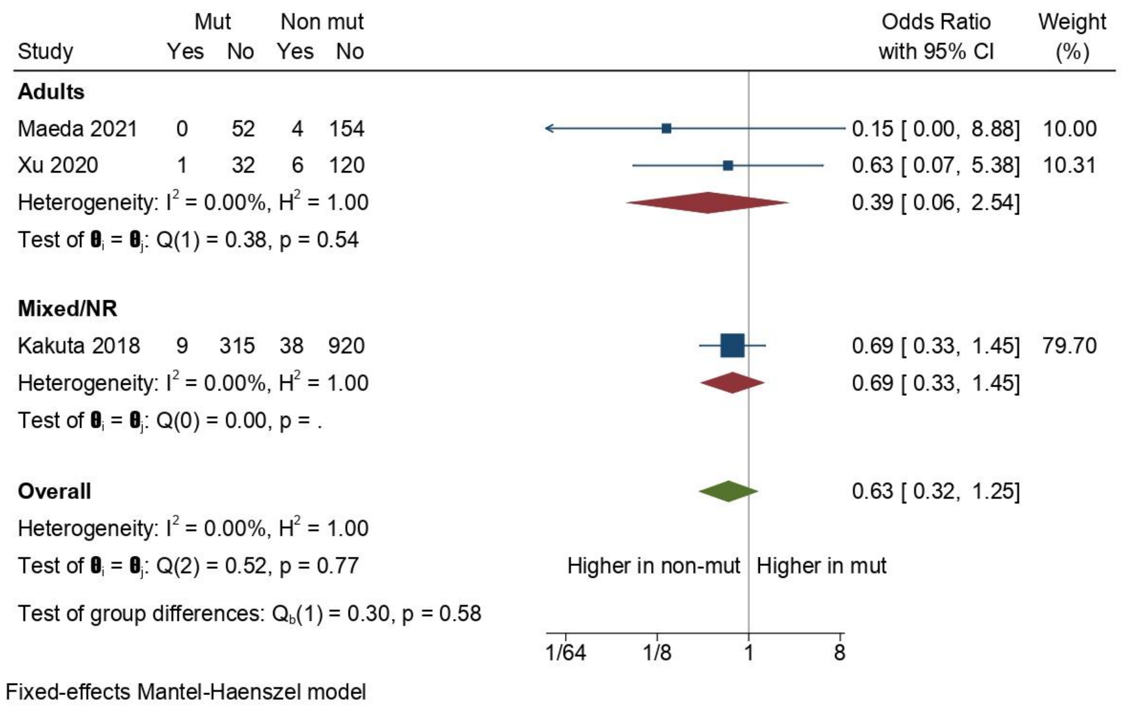


Figure S170. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Hepatotoxicity. Subgroup analysis according to age

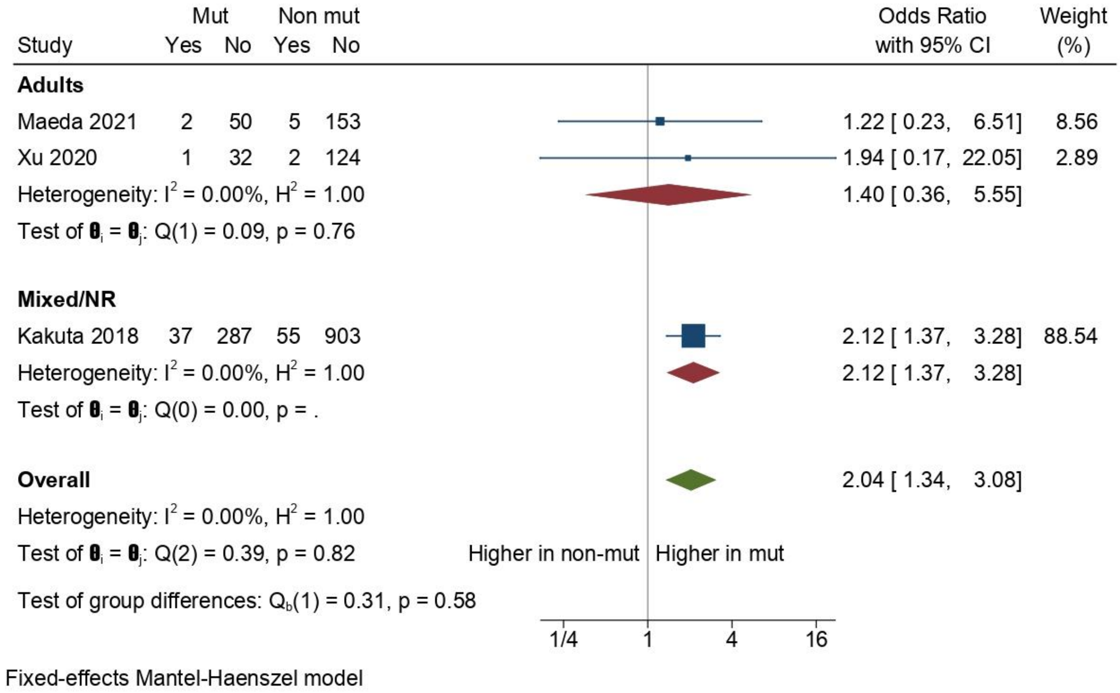


Figure S171. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Gastrointestinal side effects. Subgroup analysis according to age

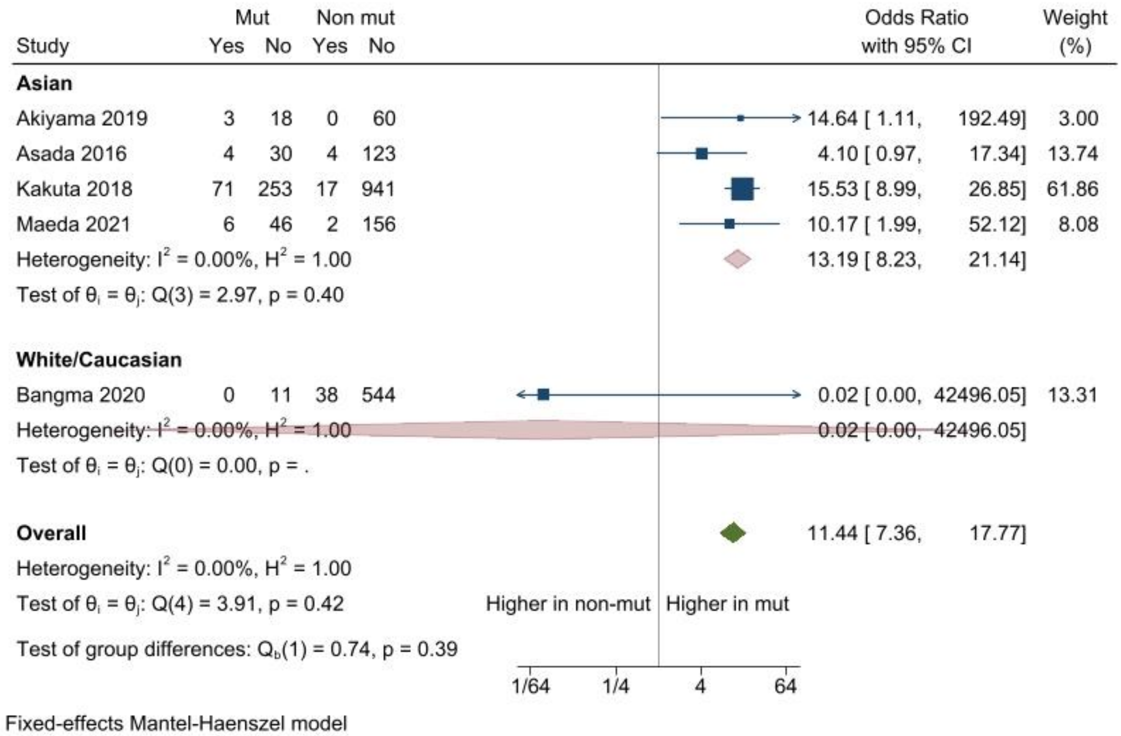


Figure S172. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Total serious adverse events. Subgroup analysis according to race

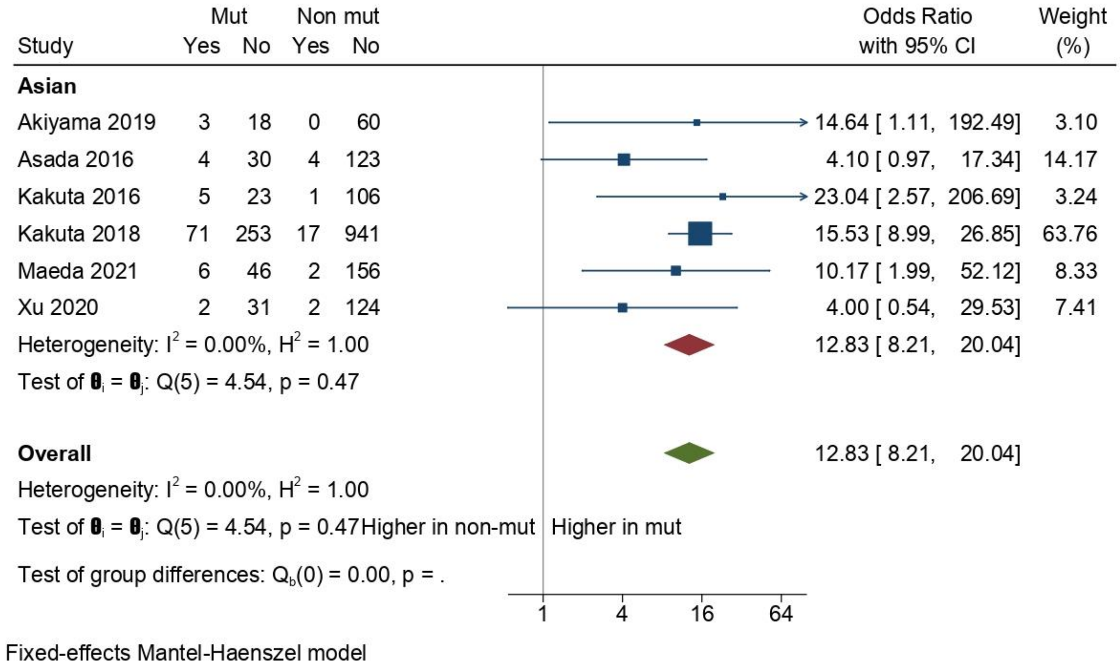


Figure S173. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Serious hematologic adverse events. Subgroup analysis according to race

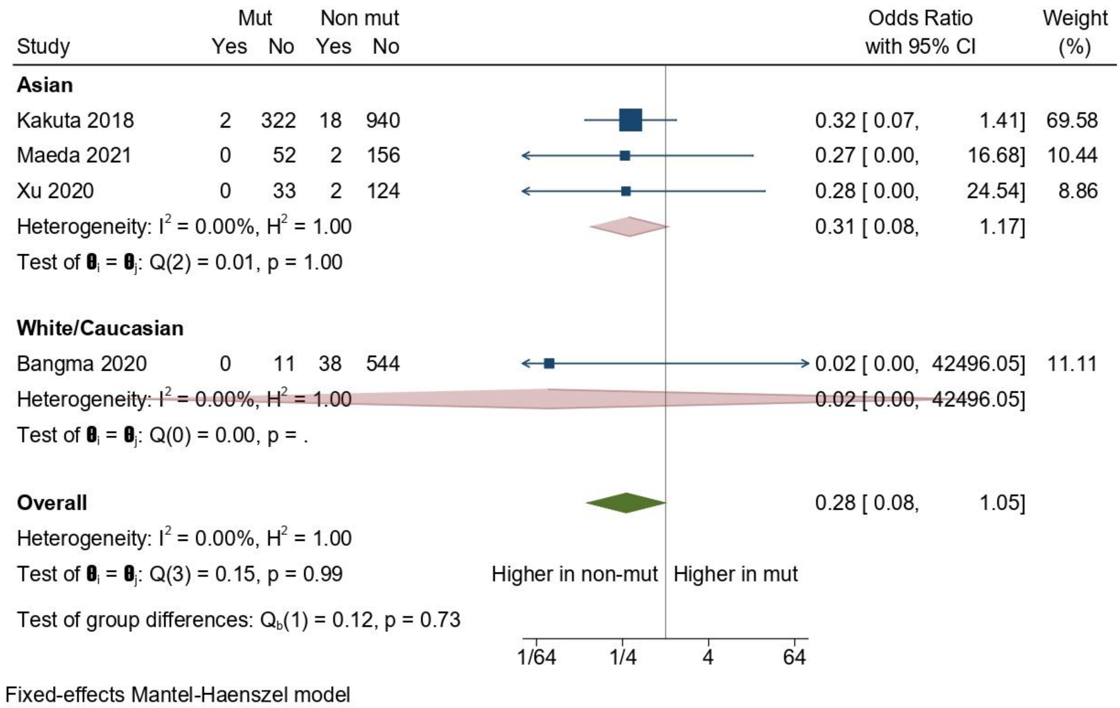


Figure S174. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Pancreatitis. Subgroup analysis according to race

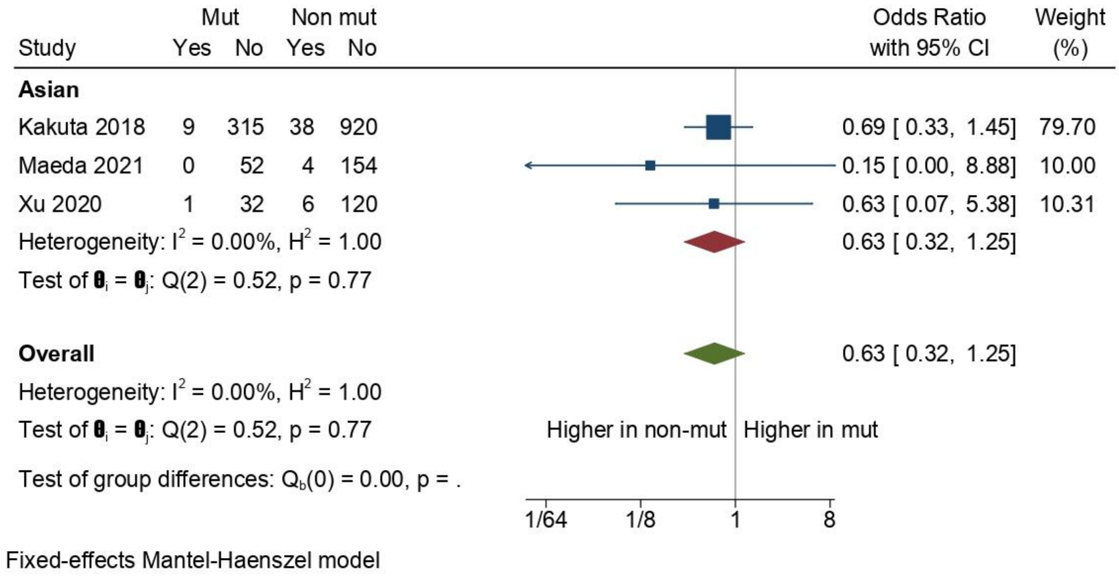


Figure S175. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Hepatotoxicity. Subgroup analysis according to race

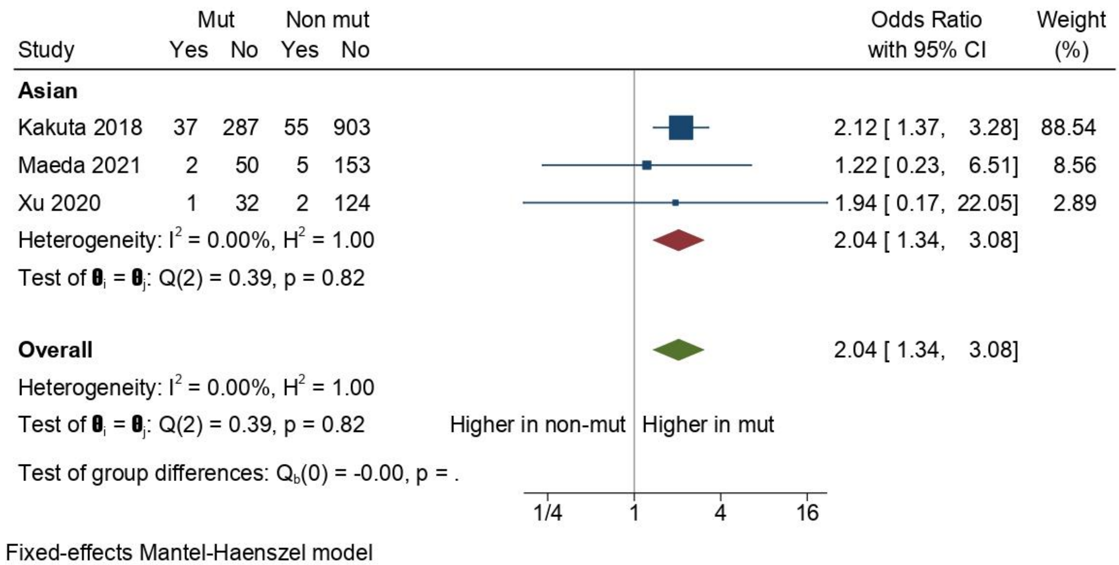


Figure S176. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Gastrointestinal side effects. Subgroup analysis according to race

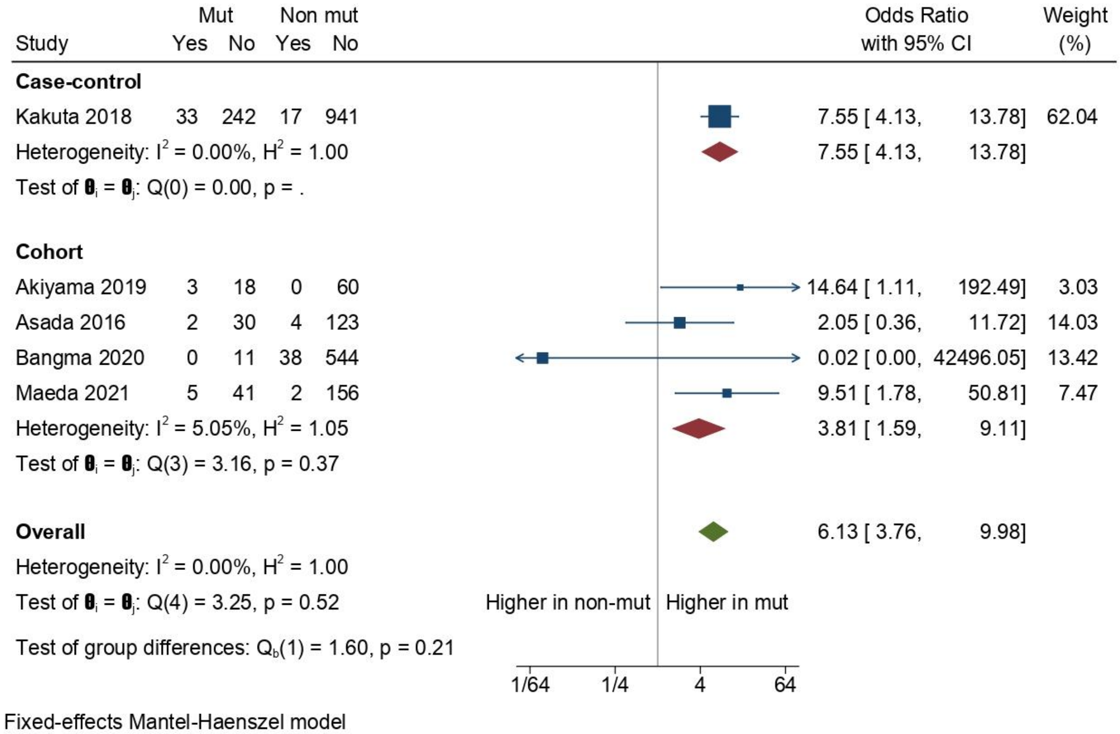


Figure S177. Forest plot of comparison heterozygous *NUDT15* vs wild-type *NUDT15*, outcome: Total serious adverse events

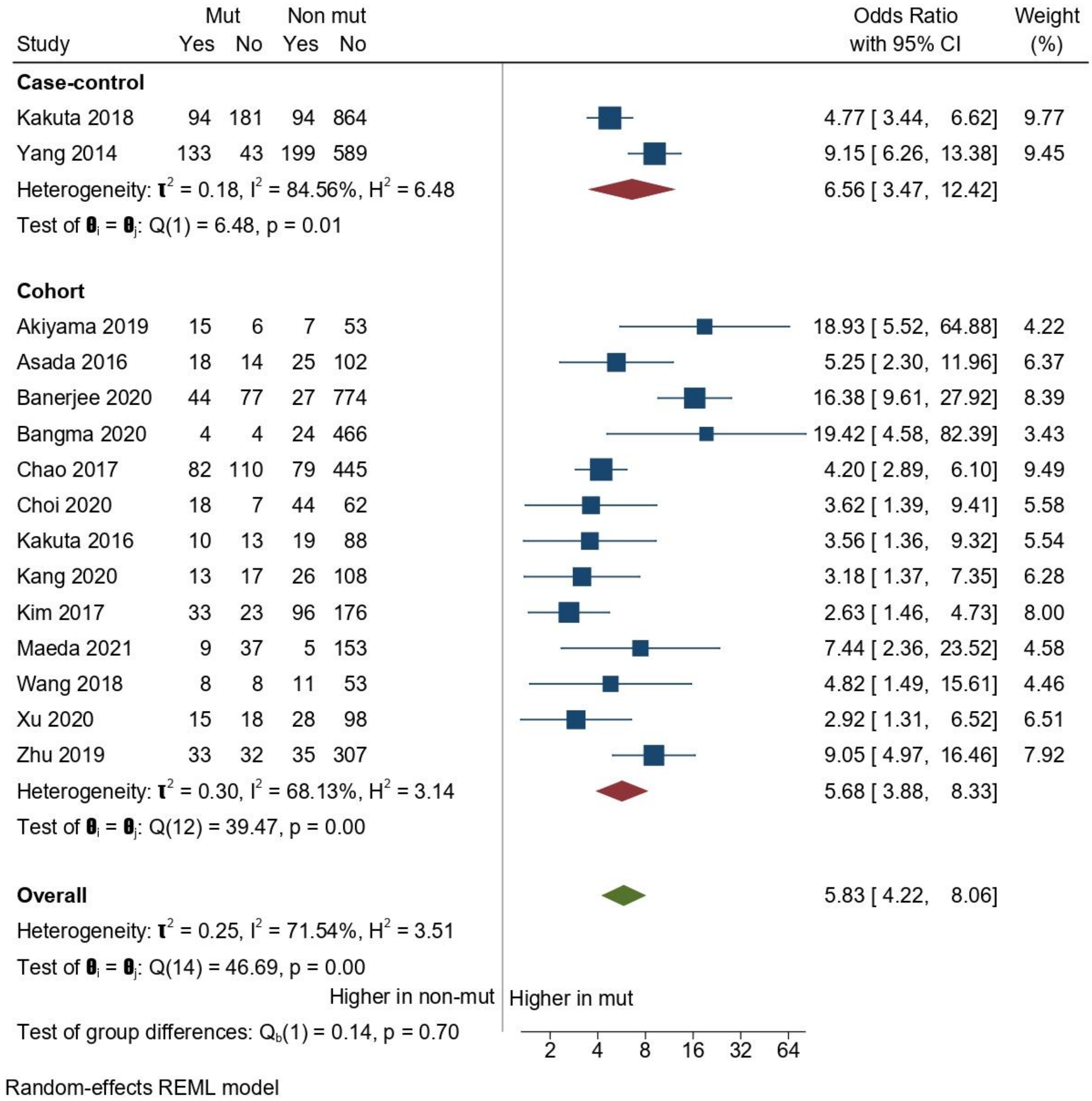


Figure S178. Forest plot of comparison heterozygous *NUDT15* vs wild-type *NUDT15*, outcome: Total hematologic adverse events

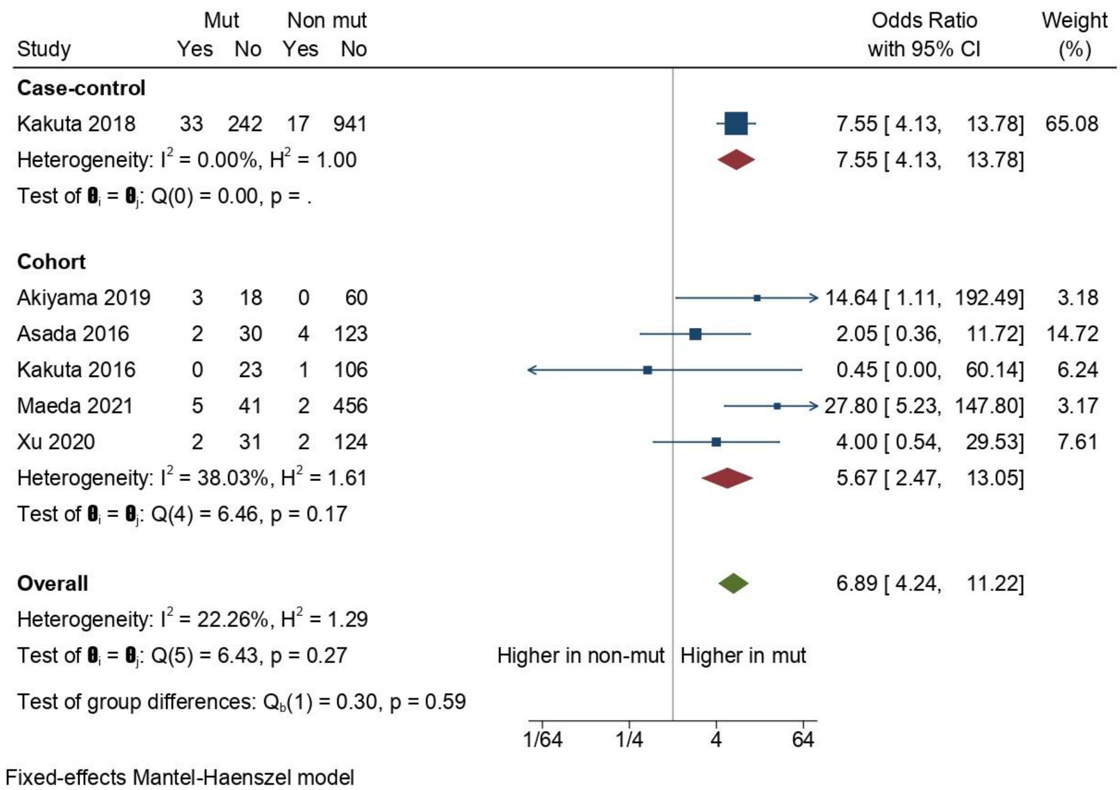


Figure S179. Forest plot of comparison heterozygous *NUDT15* vs wild-type *NUDT15*, outcome: Serious hematologic adverse events

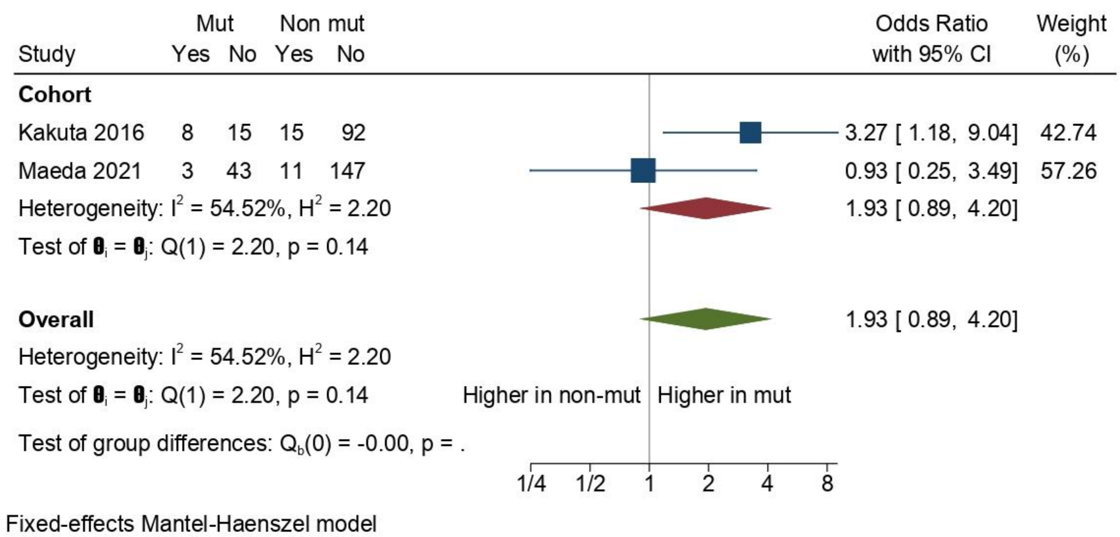


Figure S180. Forest plot of comparison heterozygous *NUDT15* vs wild-type *NUDT15*, outcome: Withdrawal due to AE

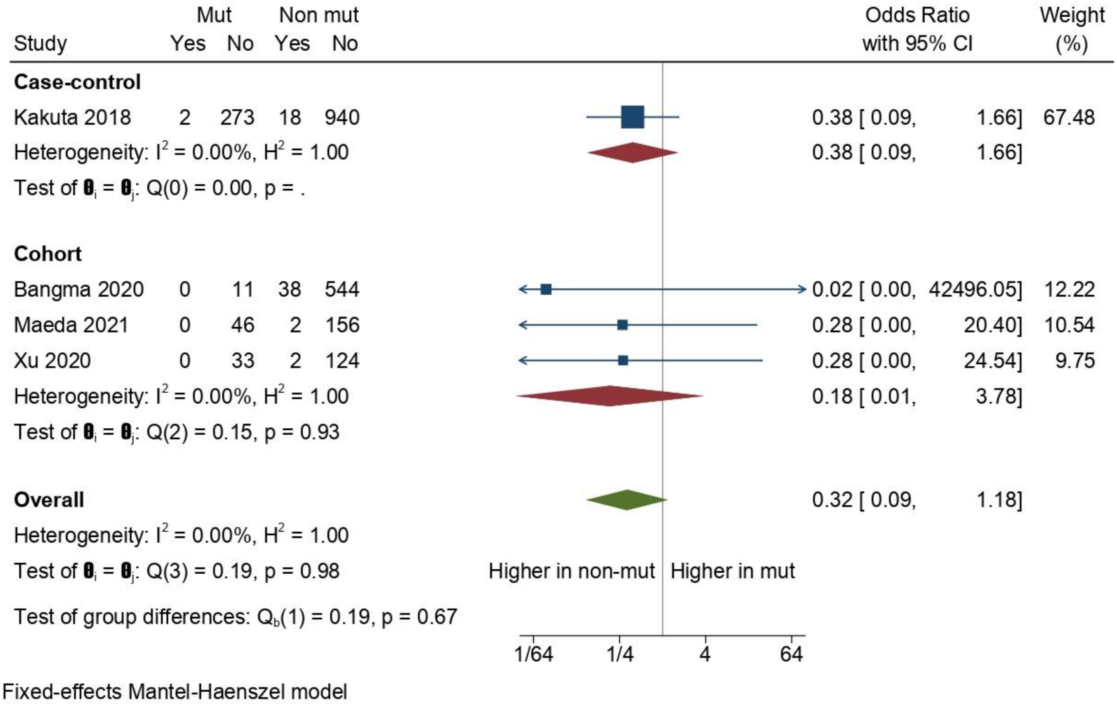


Figure S181. Forest plot of comparison heterozygous *NUDT15* vs wild-type *NUDT15*, outcome: Pancreatitis

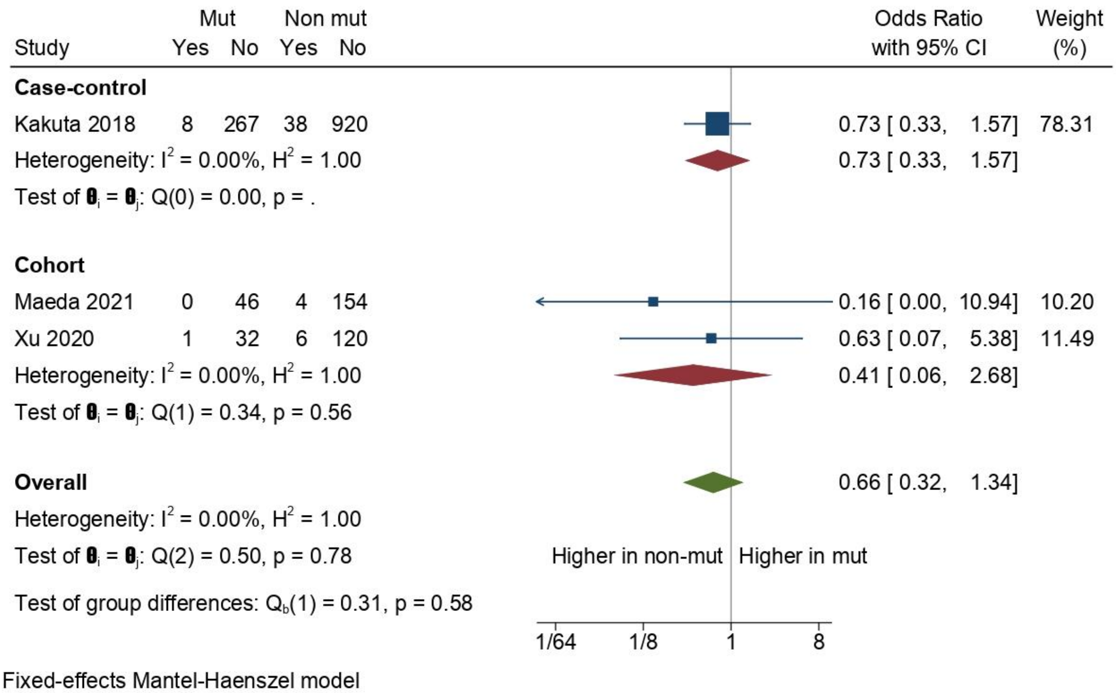


Figure S182. Forest plot of comparison heterozygous *NUDT15* vs wild-type *NUDT15*, outcome: Hepatotoxicity

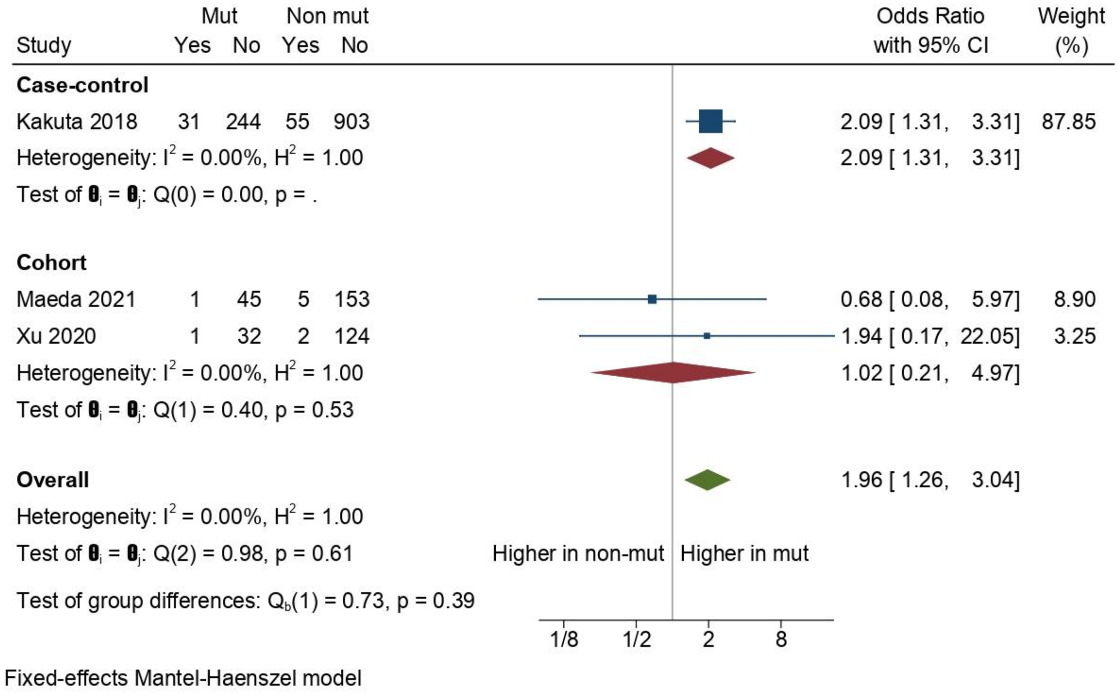


Figure S183. Forest plot of comparison heterozygous *NUDT15* vs wild-type *NUDT15*, outcome: Gastrointestinal side effects

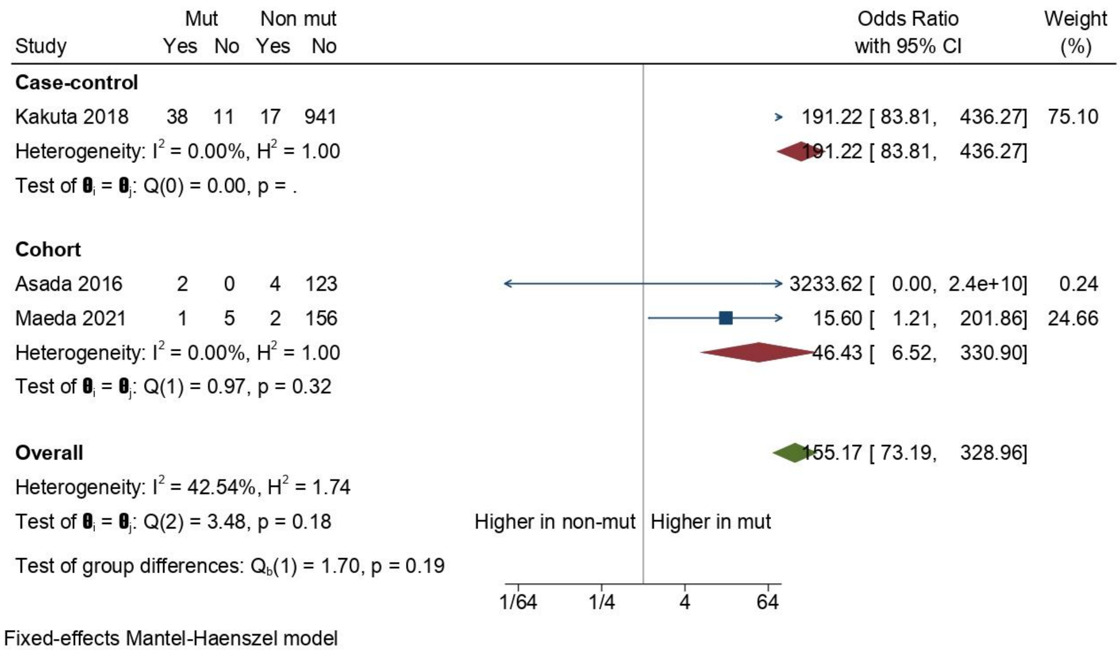


Figure S184. Forest plot of comparison 2 mutant *NUDT15* alleles vs wild-type, outcome: Total serious adverse events

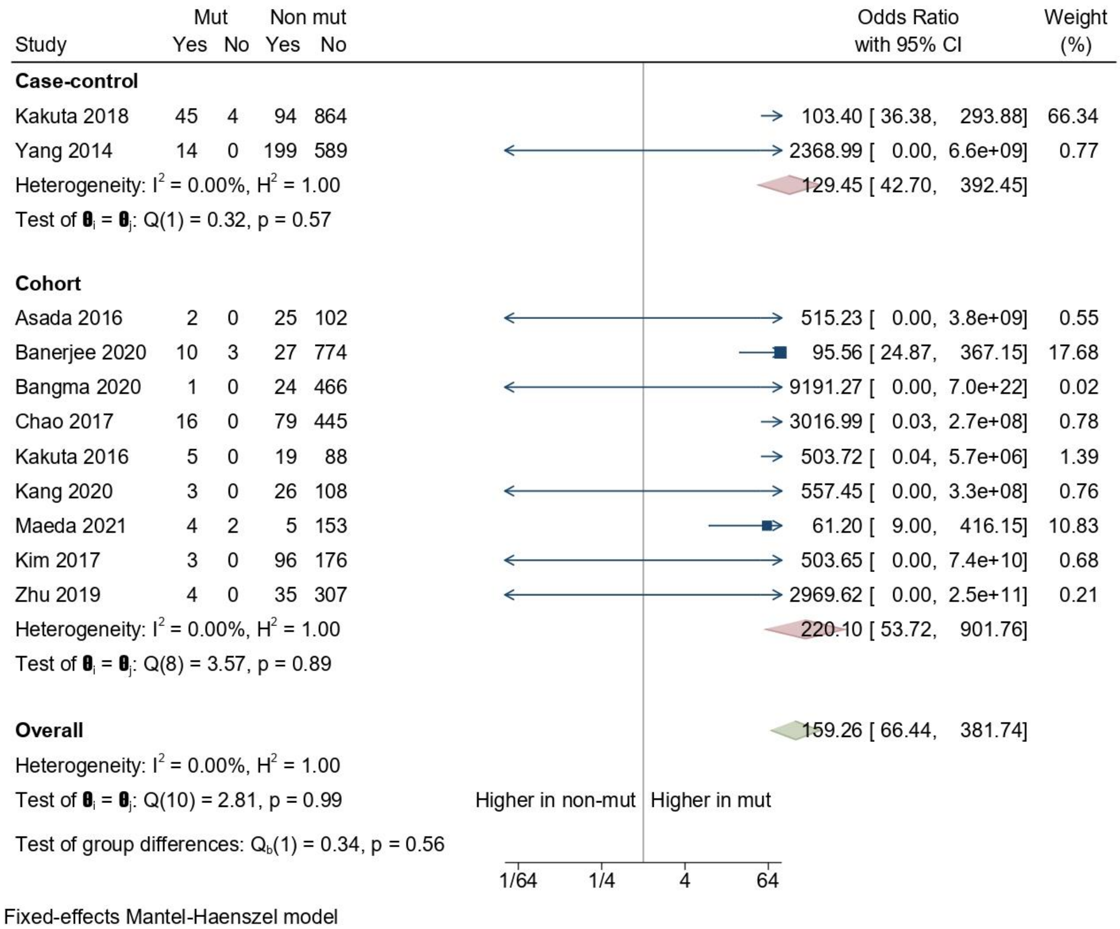


Figure S185. Forest plot of comparison 2 mutant *NUDT15* alleles vs wild-type, outcome: Total hematologic adverse events

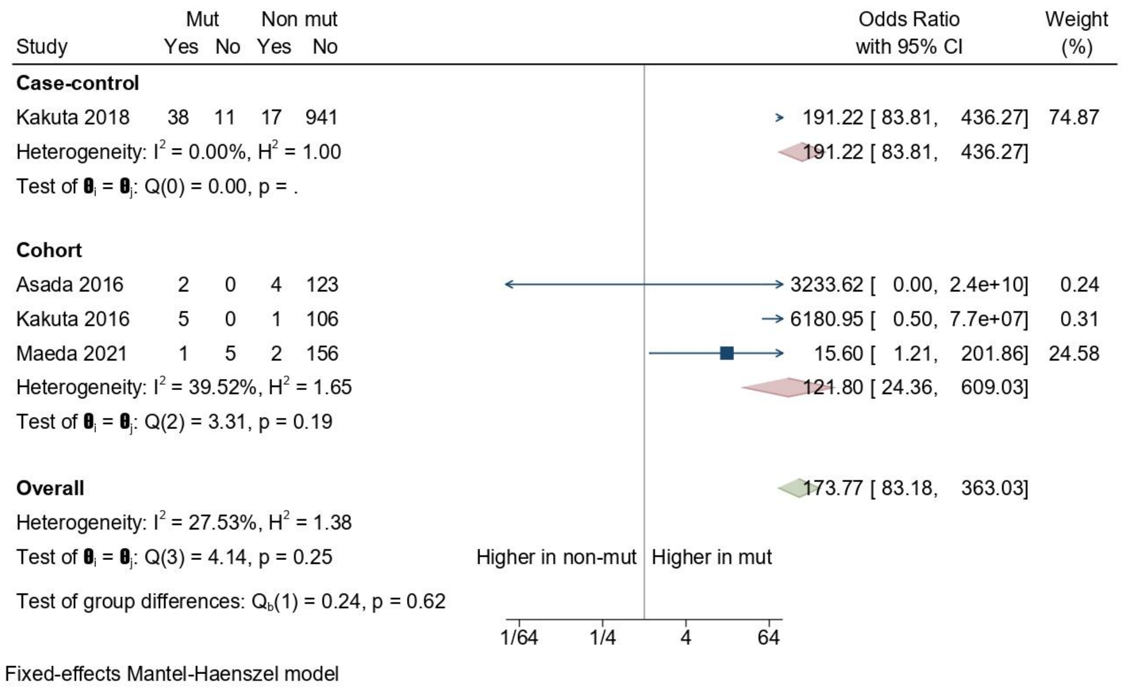


Figure S186. Forest plot of comparison 2 mutant *NUDT15* alleles vs wild-type, outcome: Serious hematologic adverse events

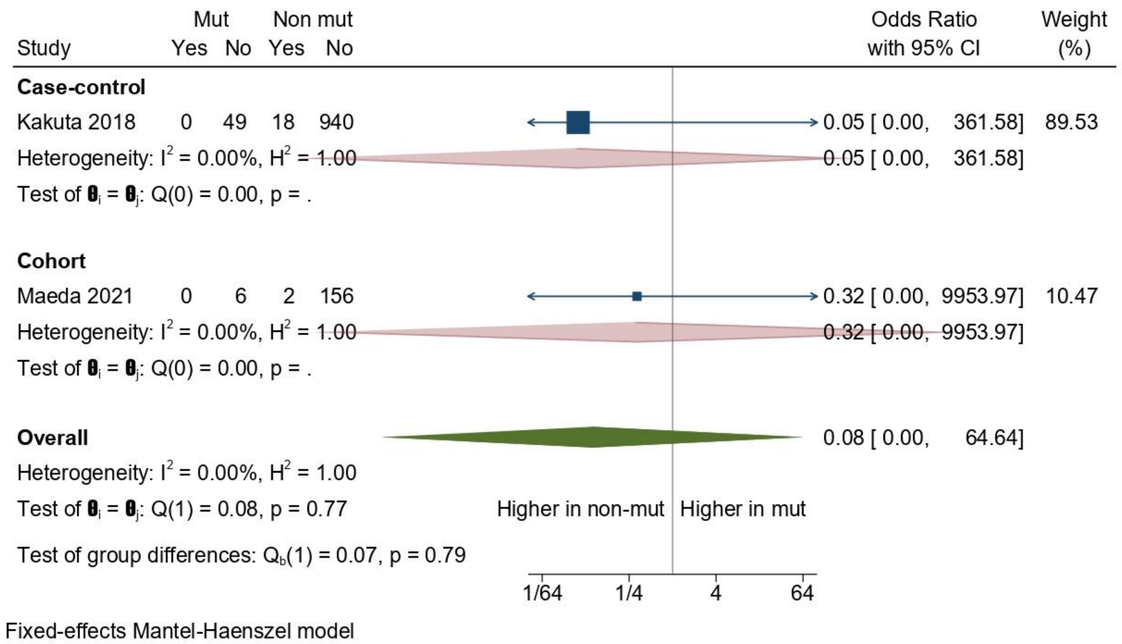


Figure S187. Forest plot of comparison 2 mutant *NUDT15* alleles vs wild-type, outcome: Pancreatitis

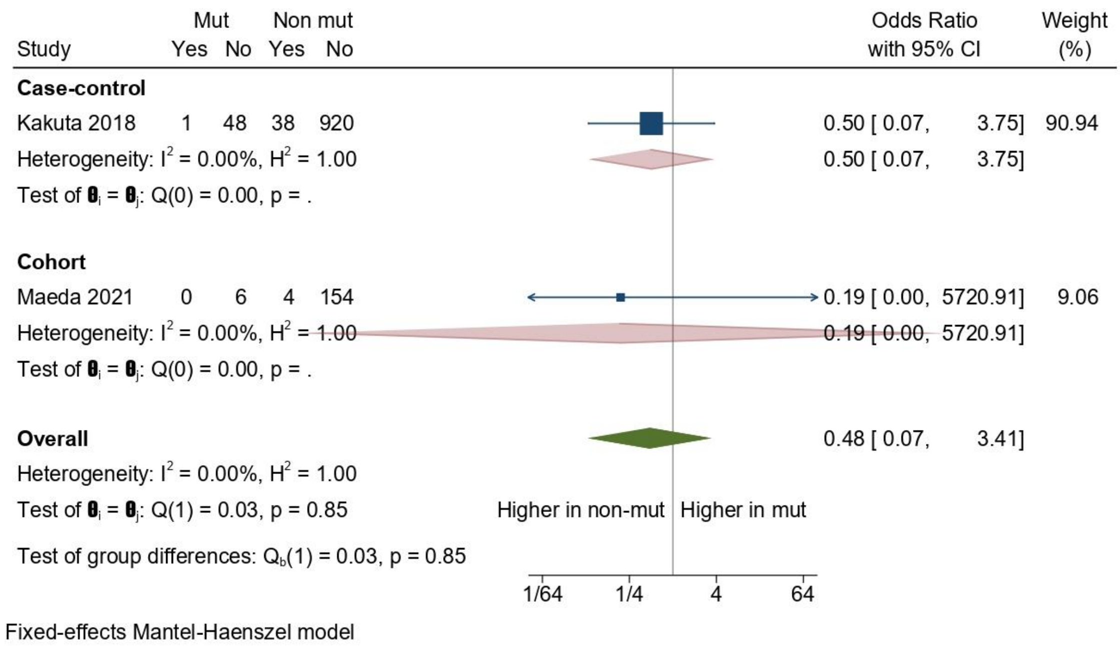


Figure S188. Forest plot of comparison 2 mutant *NUDT15* alleles vs wild-type, outcome: Hepatotoxicity

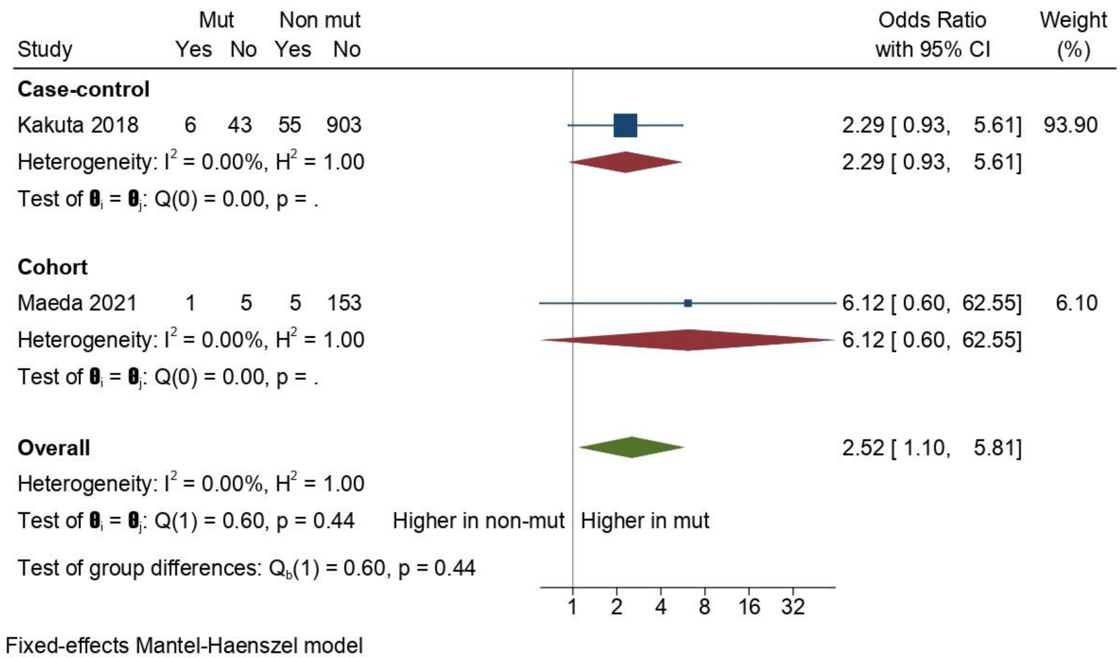


Figure S189. Forest plot of comparison 2 mutant *NUDT15* alleles vs wild-type, outcome: Gastrointestinal side effects

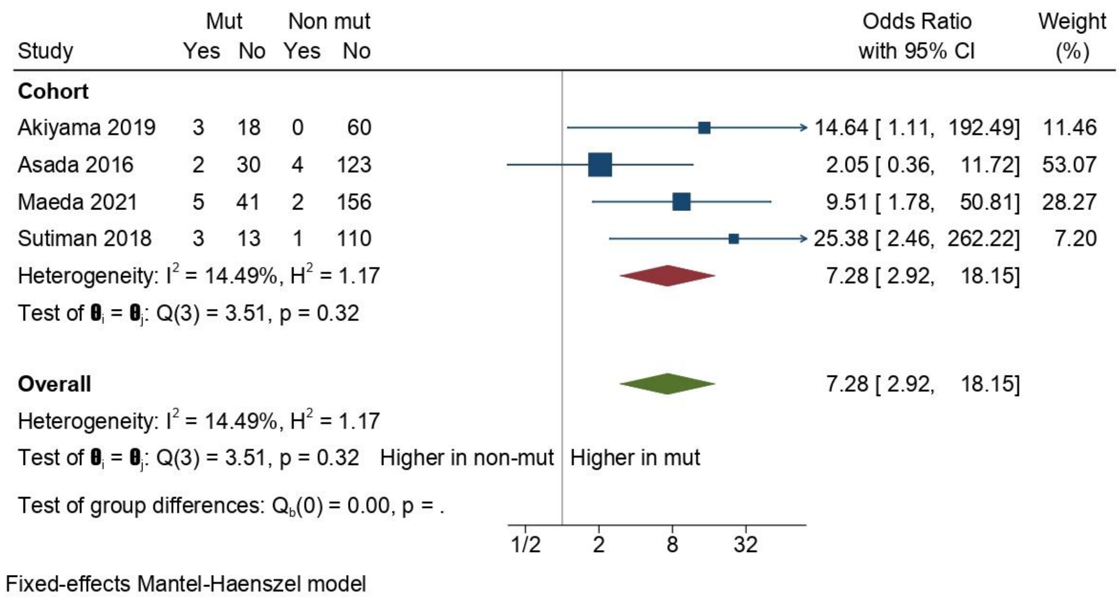


Figure S190. Forest plot of comparison *NUDT15* R139C heterozygous vs wild-type, outcome: Total serious adverse events

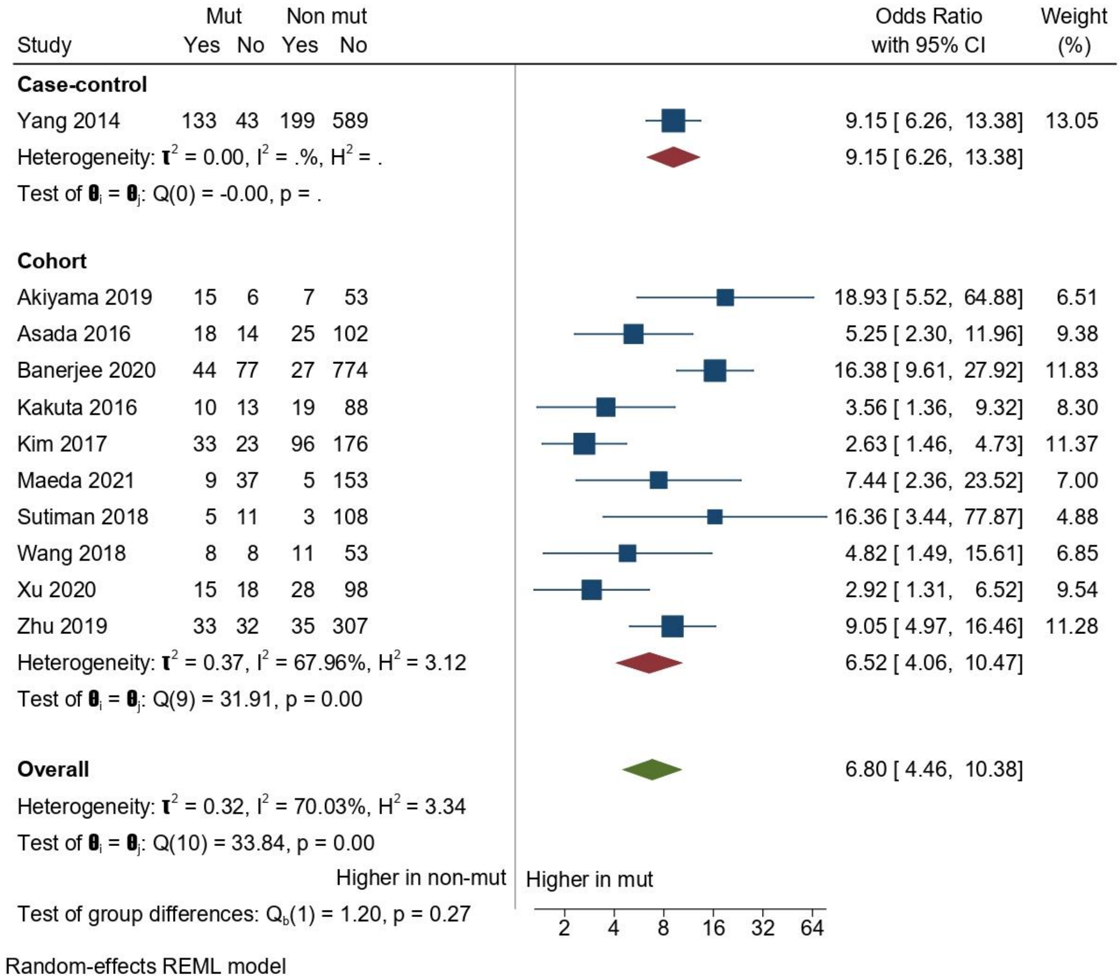


Figure S191. Forest plot of comparison *NUDT15* R139C heterozygous vs wild-type, outcome: Total hematologic adverse events

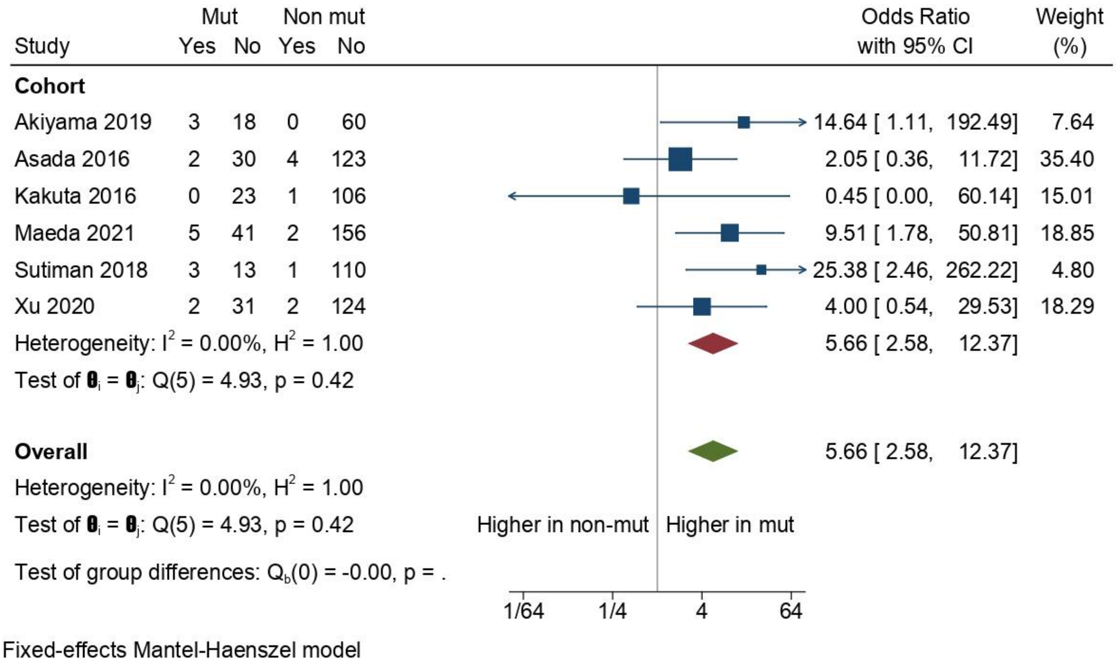


Figure S192. Forest plot of comparison *NUDT15* R139C heterozygous vs wild-type, outcome: Serious hematologic adverse events

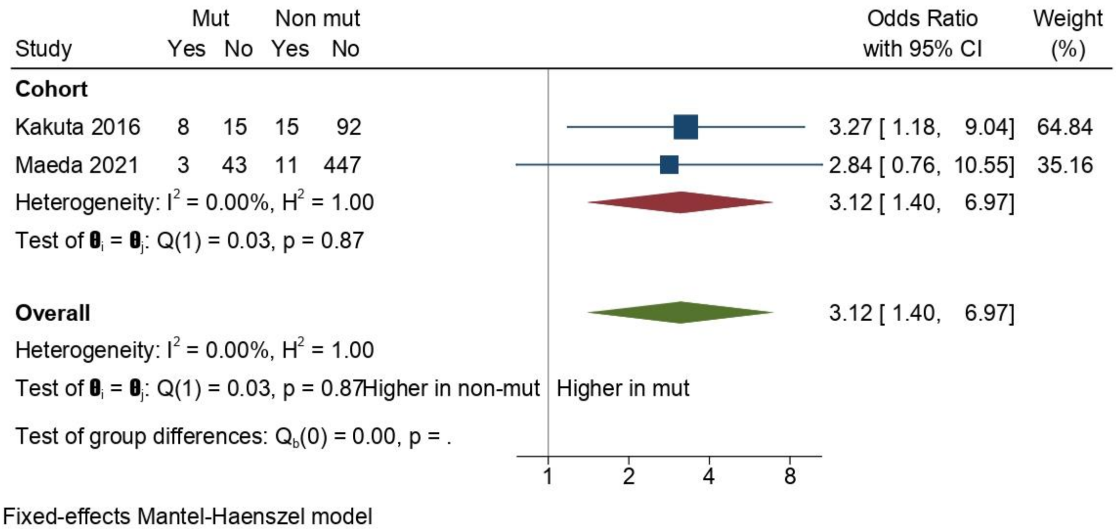


Figure S193. Forest plot of comparison *NUDT15* R139C heterozygous vs wild-type, outcome: Withdrawal due to adverse events

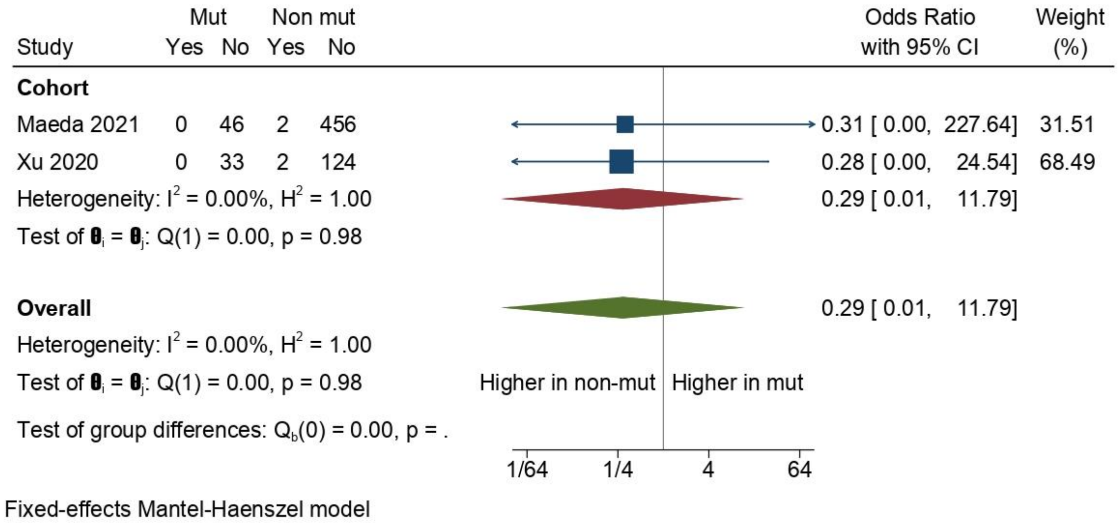


Figure S194. Forest plot of comparison *NUDT15* R139C heterozygous vs wild-type, outcome: Pancreatitis

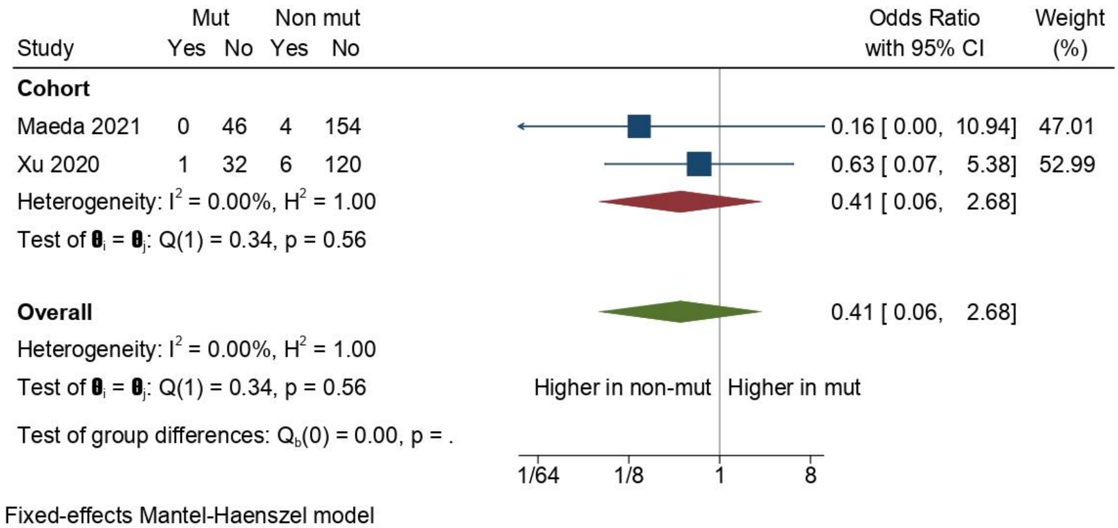


Figure S195. Forest plot of comparison *NUDT15* R139C heterozygous vs wild-type, outcome: Hepatotoxicity

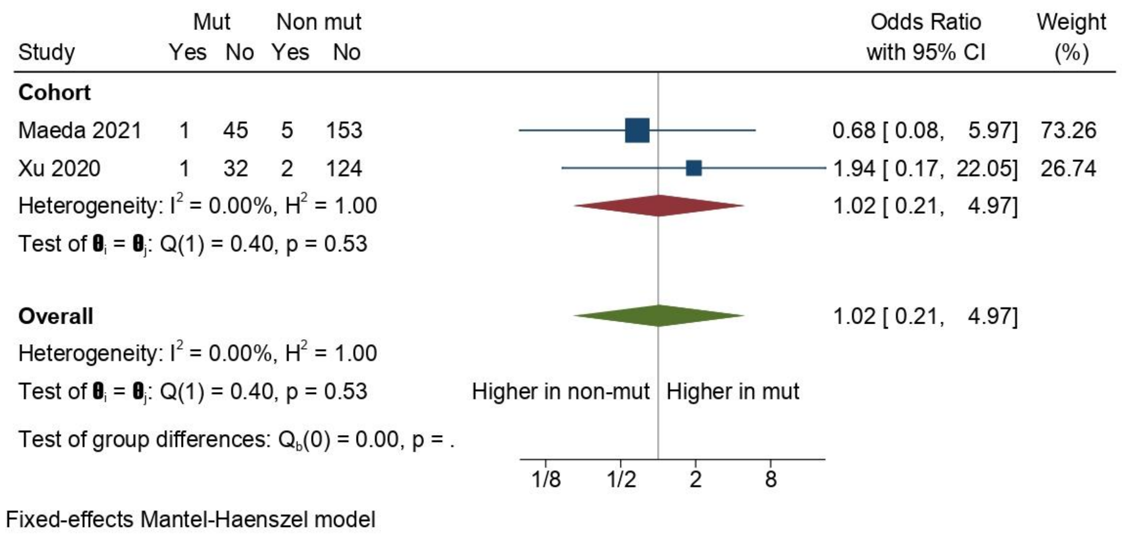


Figure S196. Forest plot of comparison *NUDT15* R139C heterozygous vs wild-type, outcome: Gastrointestinal side effects

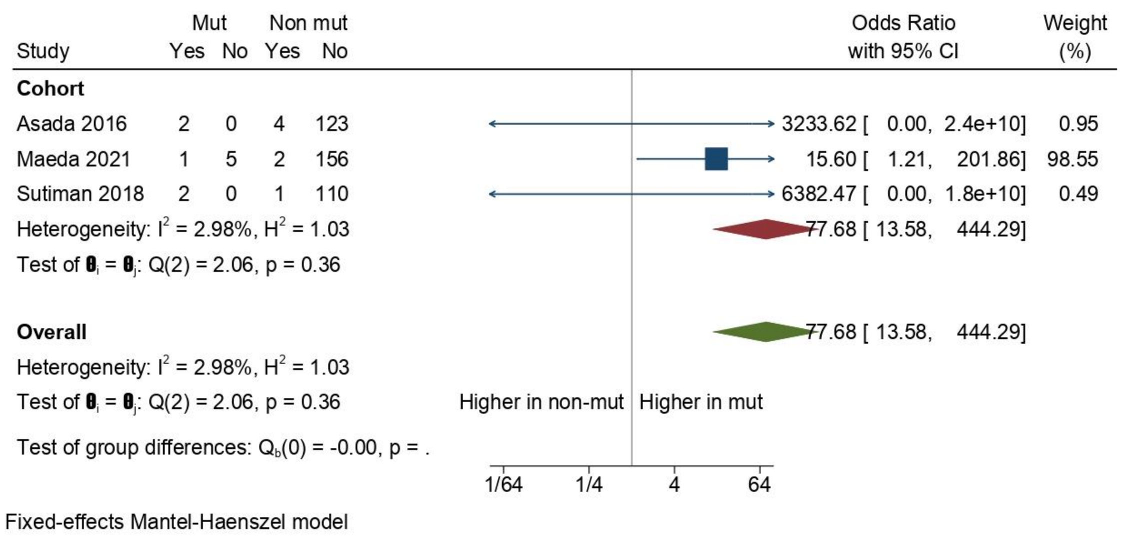


Figure S197. Forest plot of comparison *NUDT15* R139C, 2 mutant alleles vs wild-type, outcome: Total serious adverse events

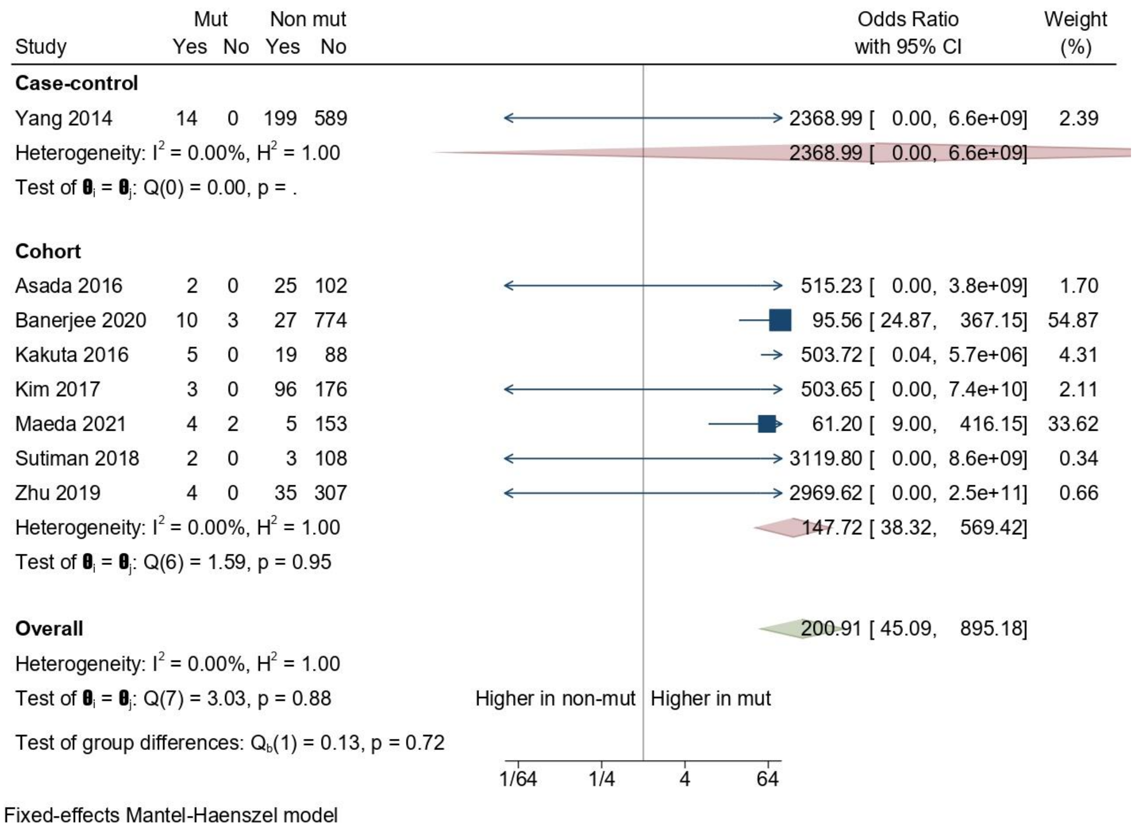


Figure S198. Forest plot of comparison *NUDT15* R139C, 2 mutant alleles vs wild-type, outcome: Total hematologic adverse events

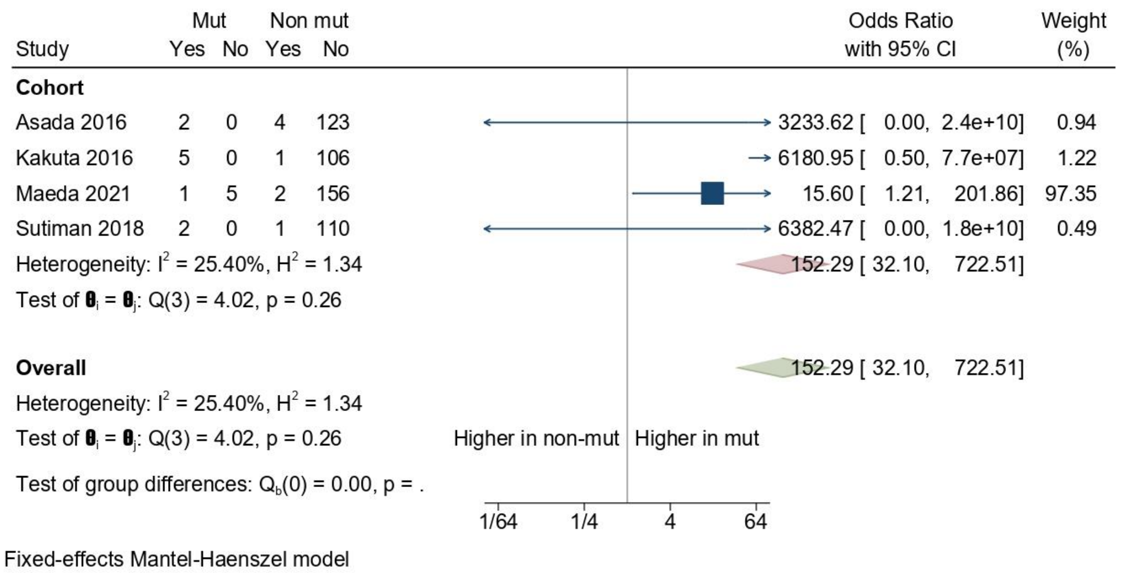


Figure S199. Forest plot of comparison *NUDT15* R139C, 2 mutant alleles vs wild-type, outcome: Serious hematologic adverse events

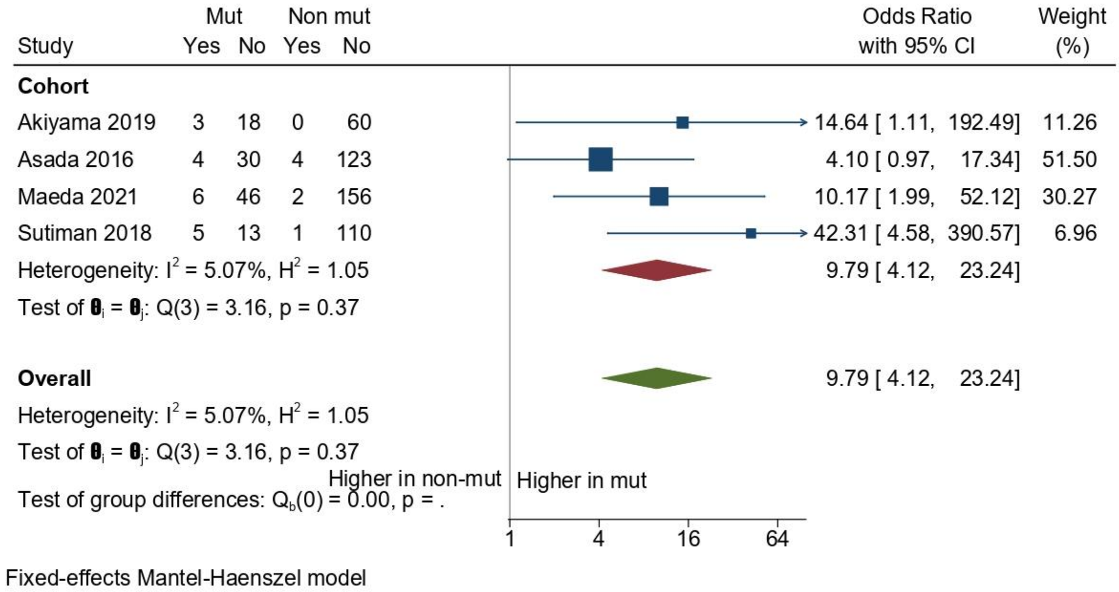


Figure S200. Forest plot of comparison *NUDT15* R139C vs wild-type, outcome: Total serious adverse events

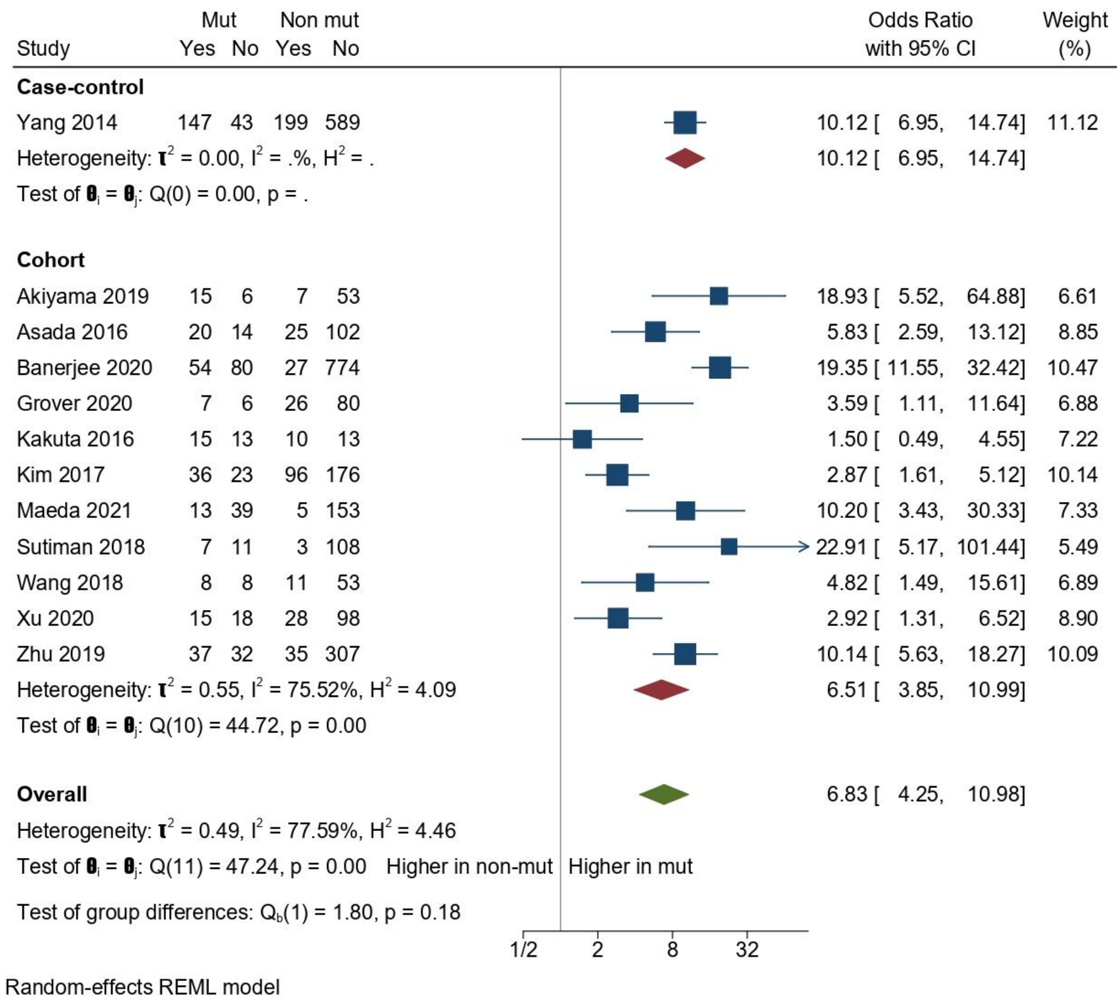


Figure S201. Forest plot of comparison *NUDT15* R139C vs wild-type, outcome: Total hematologic adverse events

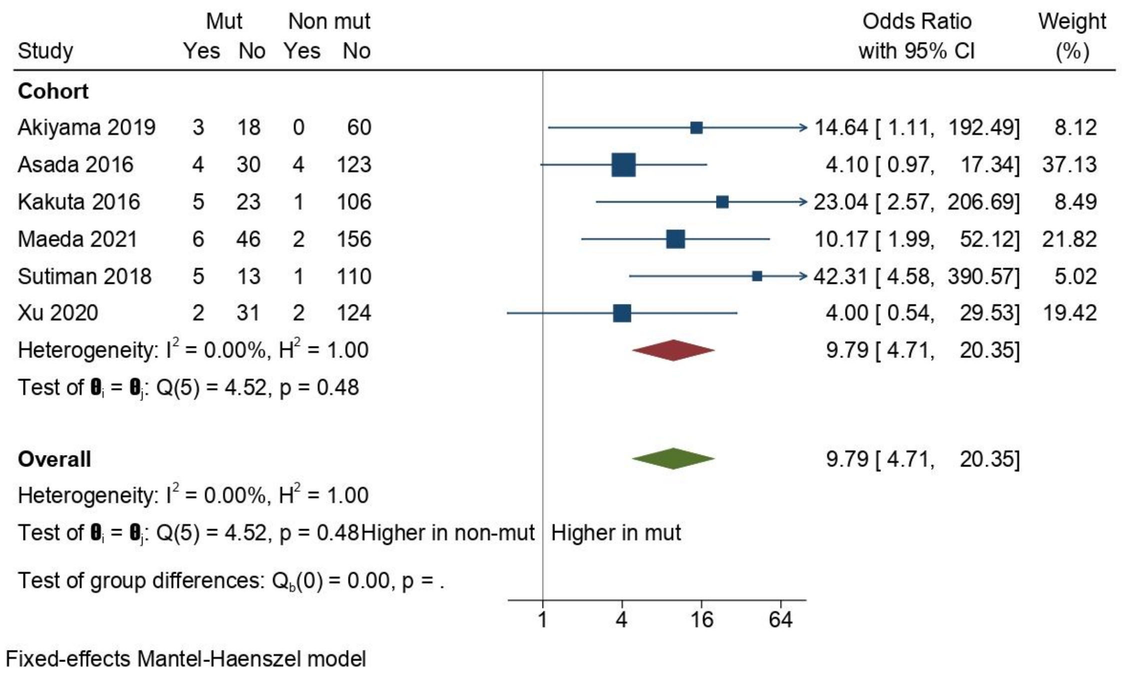


Figure S202. Forest plot of comparison *NUDT15* R139C vs wild-type, outcome: Serious hematologic adverse events

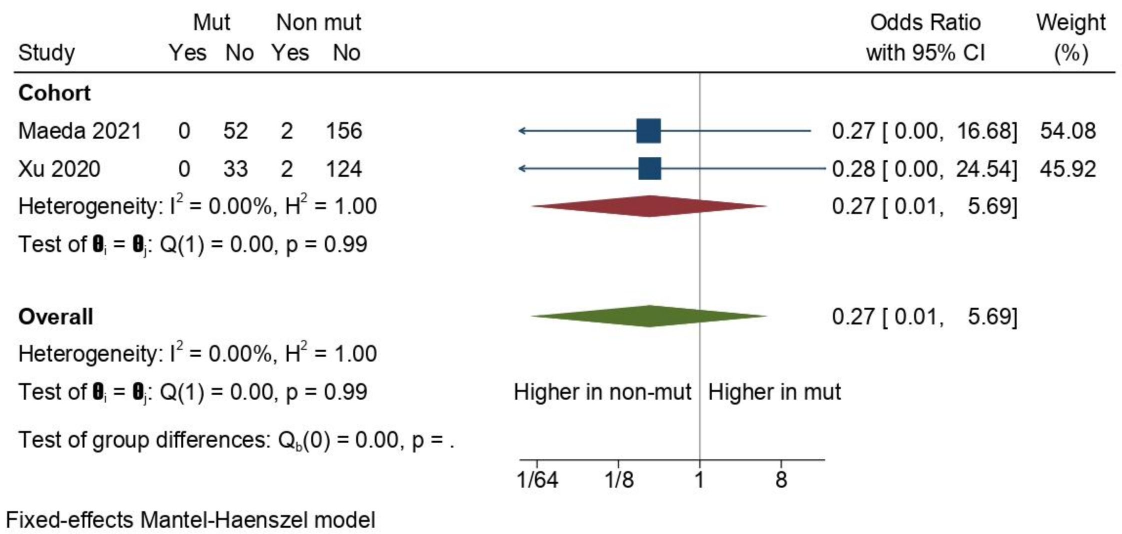


Figure S203. Forest plot of comparison *NUDT15* R139C vs wild-type, outcome: Pancreatitis

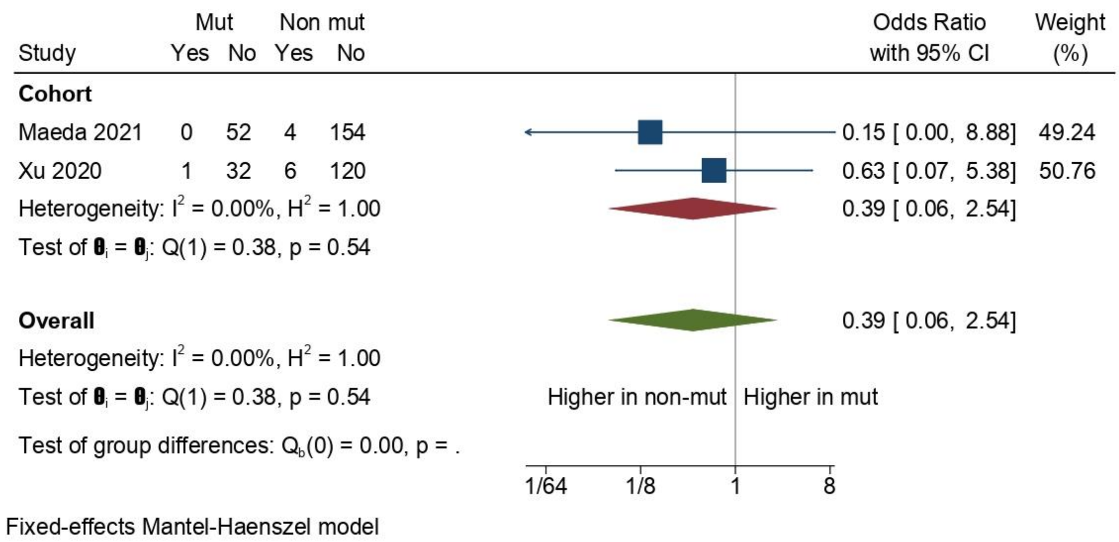


Figure S204. Forest plot of comparison *NUDT15* R139C vs wild-type, outcome: Hepatotoxicity

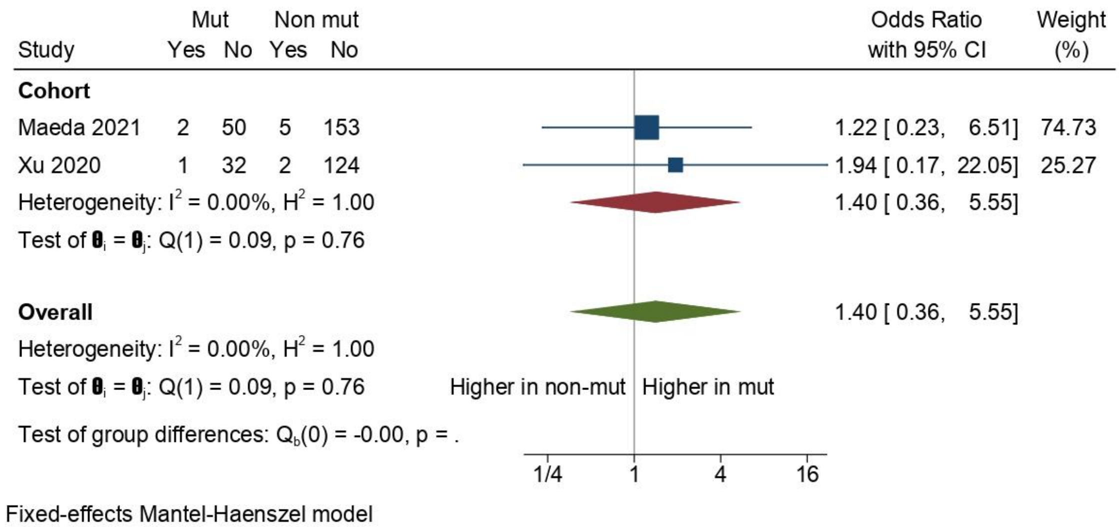


Figure S205. Forest plot of comparison *NUDT15* R139C vs wild-type, outcome: Gastrointestinal side effects

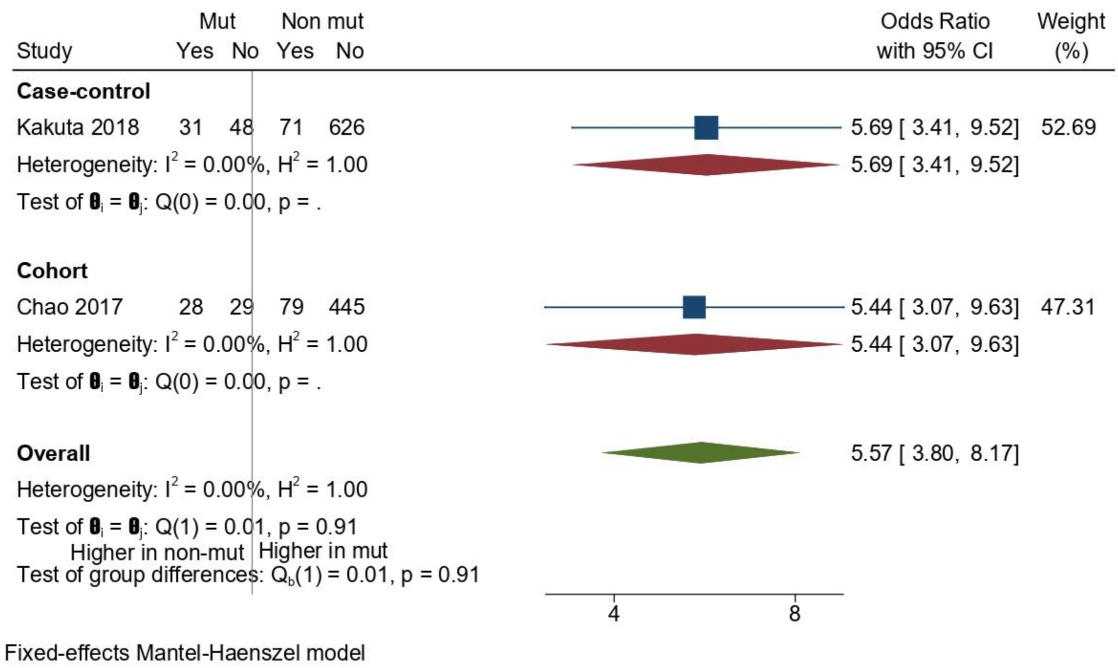


Figure S206. Forest plot of comparison *NUDT152 heterozygous vs wild-type, outcome: Total hematologic adverse events**

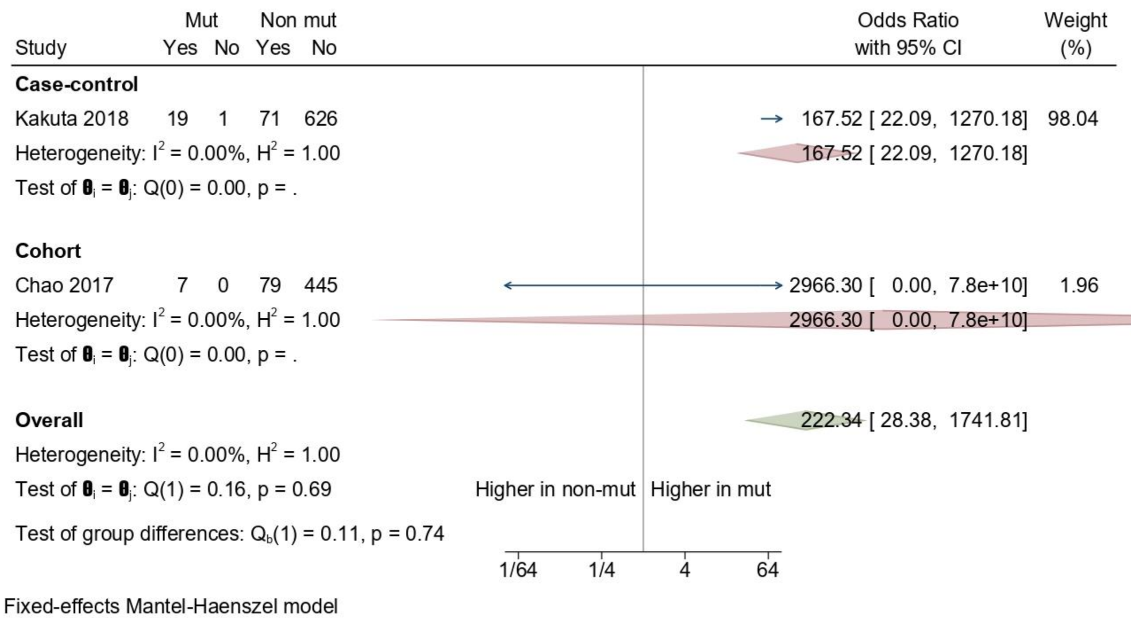


Figure S207. Forest plot of comparison *NUDT152 2 mutant alleles vs wild-type, outcome: Total hematologic adverse events**

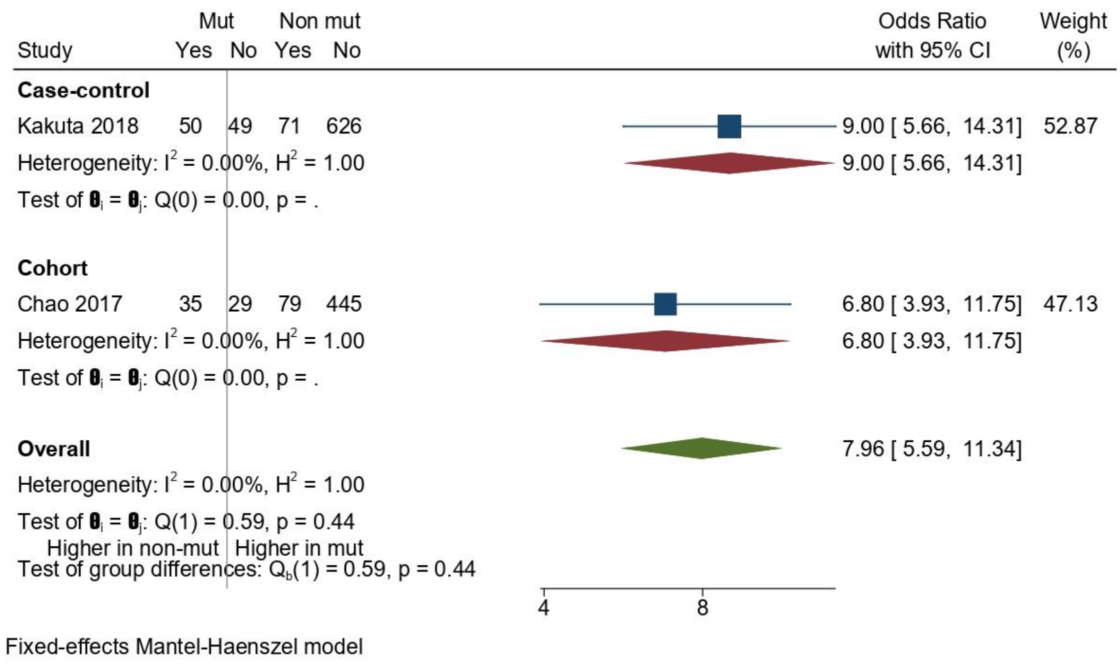


Figure S208. Forest plot of comparison *NUDT152 vs wild-type, outcome: Total hematologic adverse events**

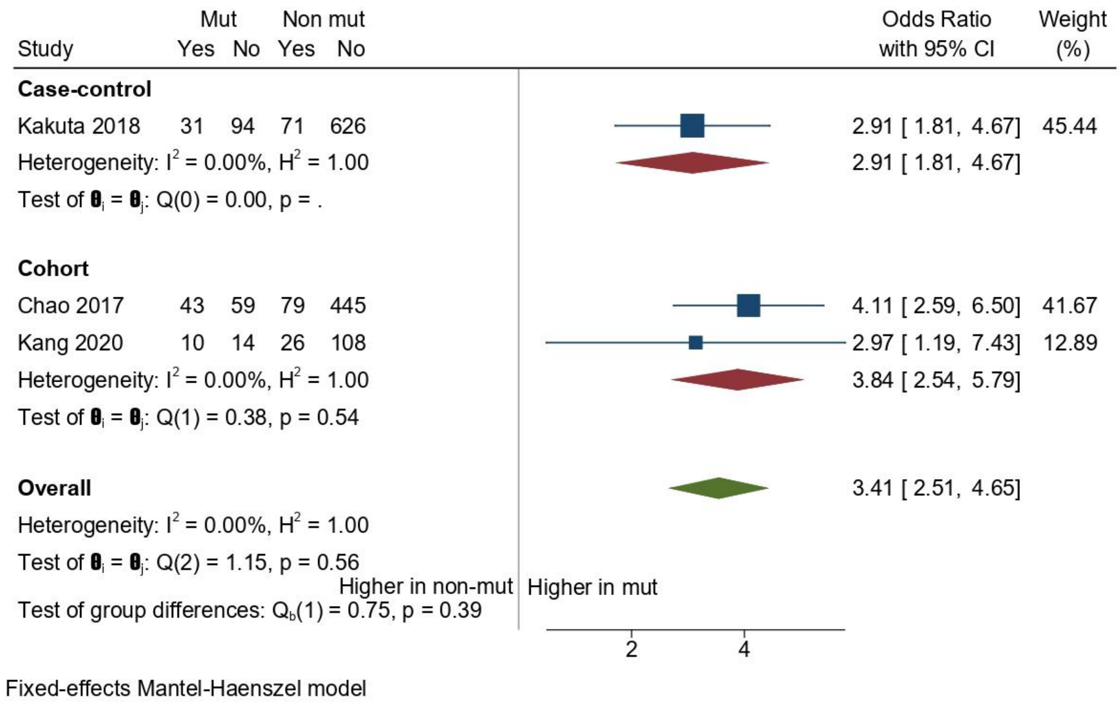


Figure S209. Forest plot of comparison *NUDT153 heterozygous vs wild-type, outcome: Total hematologic adverse events**

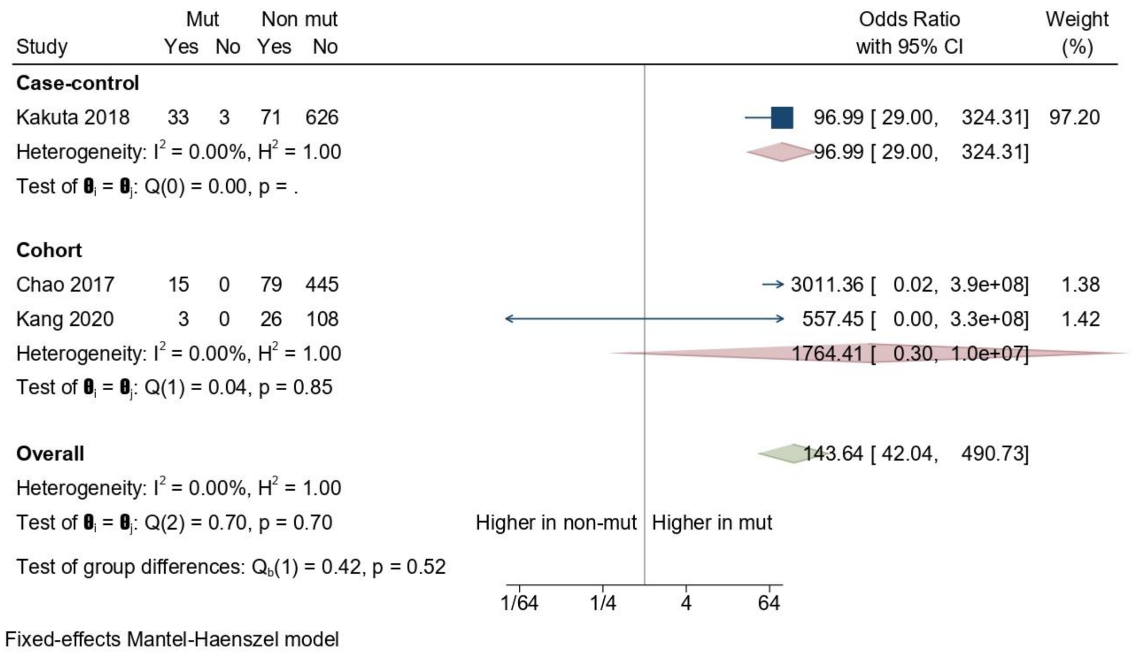


Figure S210. Forest plot of comparison *NUDT153 2 mutant alleles vs wild-type, outcome: Total hematologic adverse events**

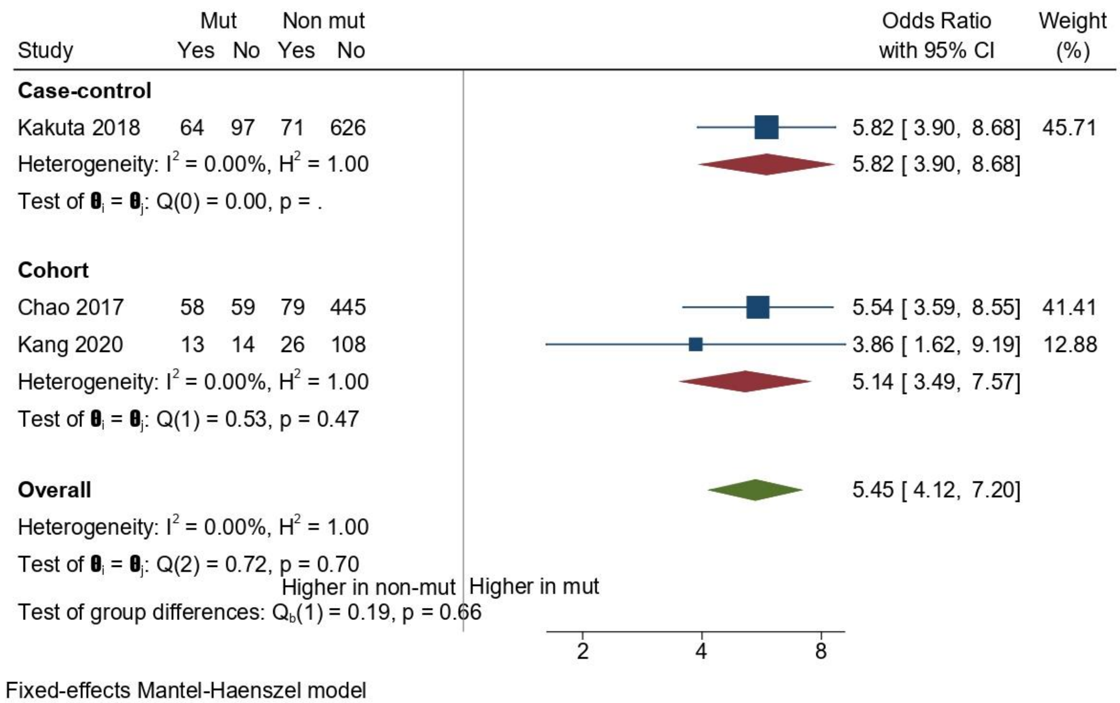


Figure S211. Forest plot of comparison *NUDT153 vs wild-type, outcome: Total hematologic adverse events**

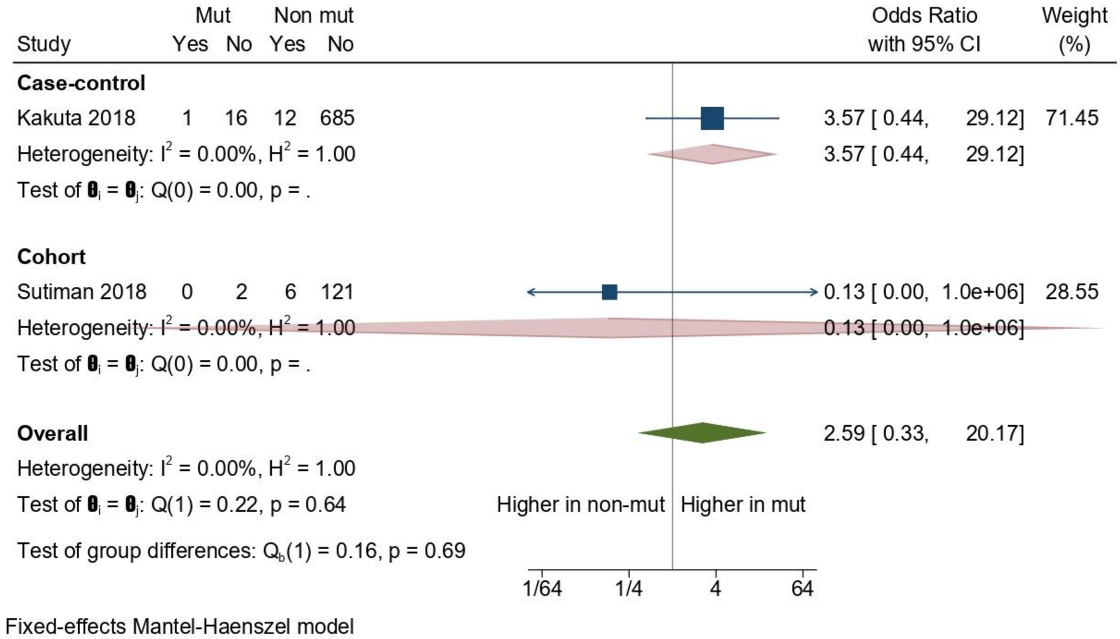


Figure S212. Forest plot of comparison *NUDT155 heterozygous vs wild-type, outcome: Total serious adverse events**

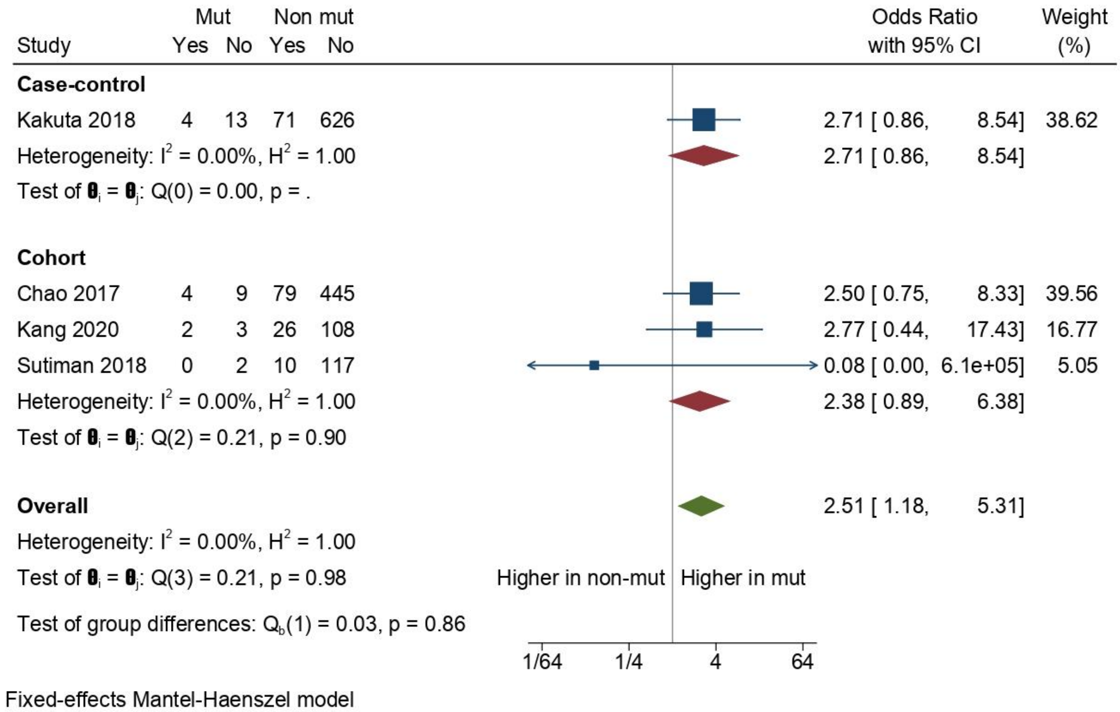


Figure S213. Forest plot of comparison *NUDT155 heterozygous vs wild-type, outcome: Total hematologic adverse events**

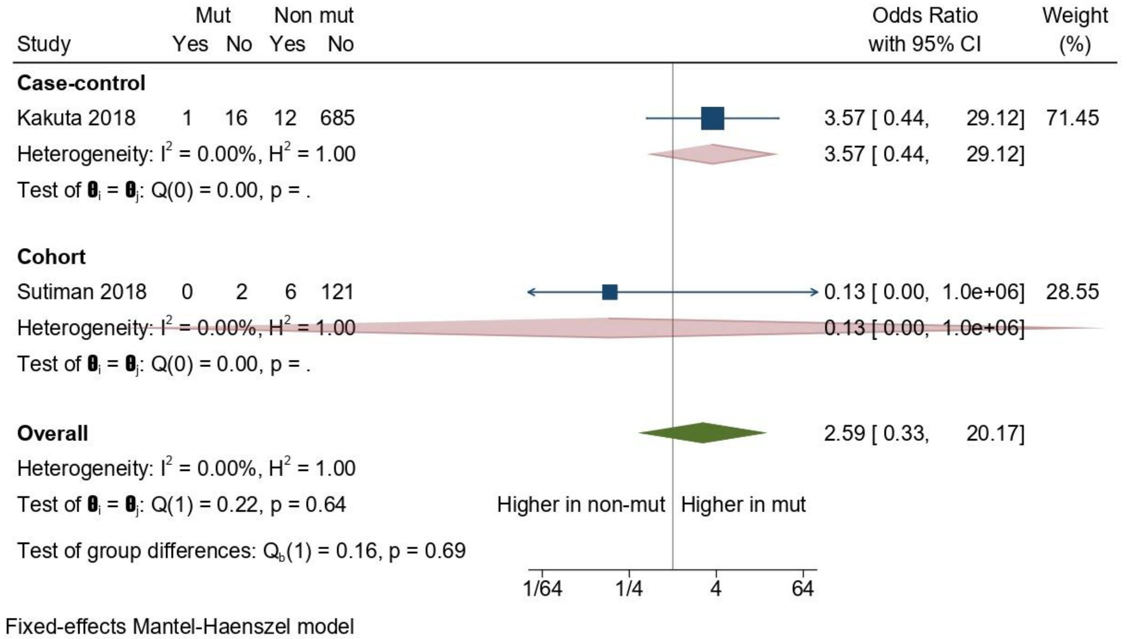


Figure S214. Forest plot of comparison *NUDT155 heterozygous vs wild-type, outcome: Serious hematologic adverse events**

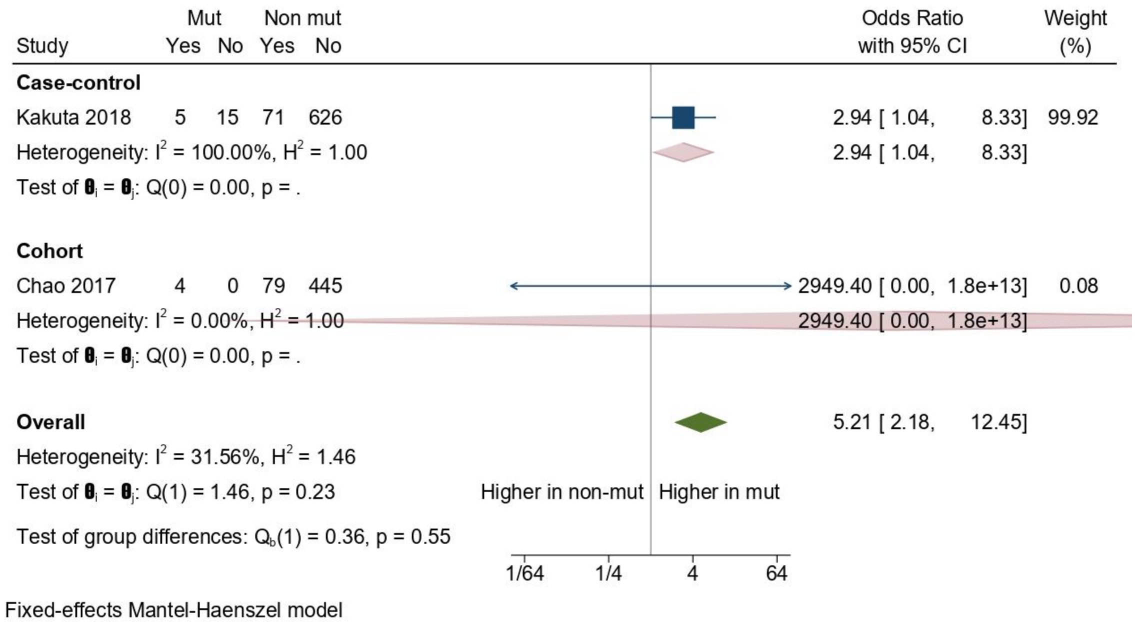


Figure S215. Forest plot of comparison *NUDT155 2 mutant alleles vs wild-type, outcome: Total hematologic adverse events**

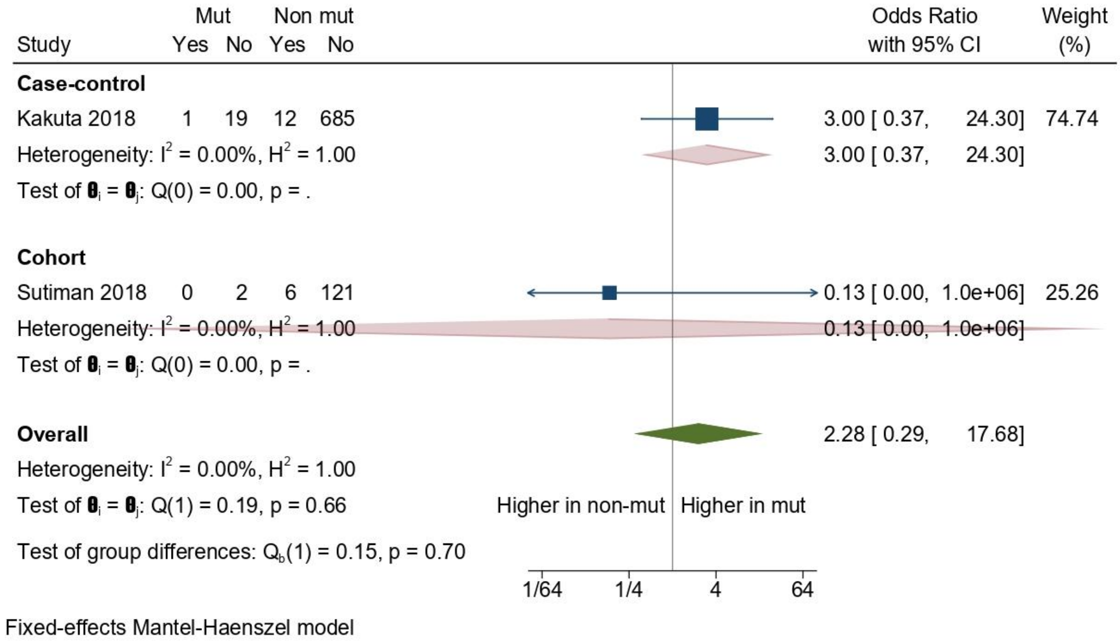


Figure S216. Forest plot of comparison *NUDT155 vs wild-type, outcome: Total serious adverse events**

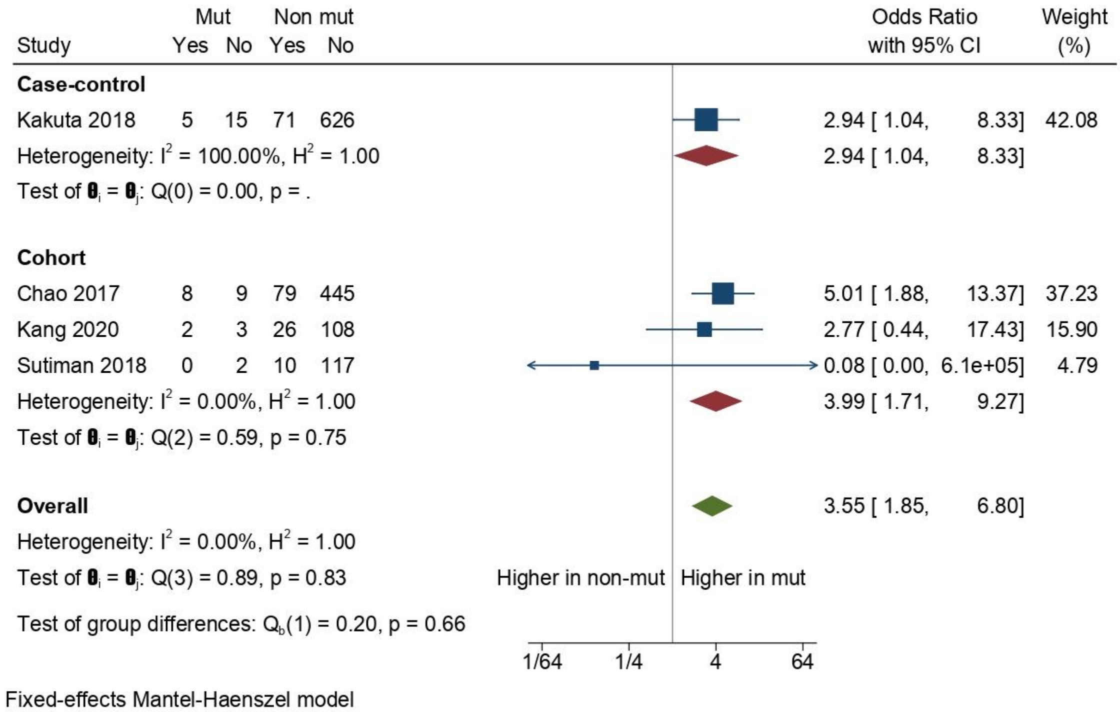


Figure S217. Forest plot of comparison *NUDT155 vs wild-type, outcome: Total hematologic adverse events**

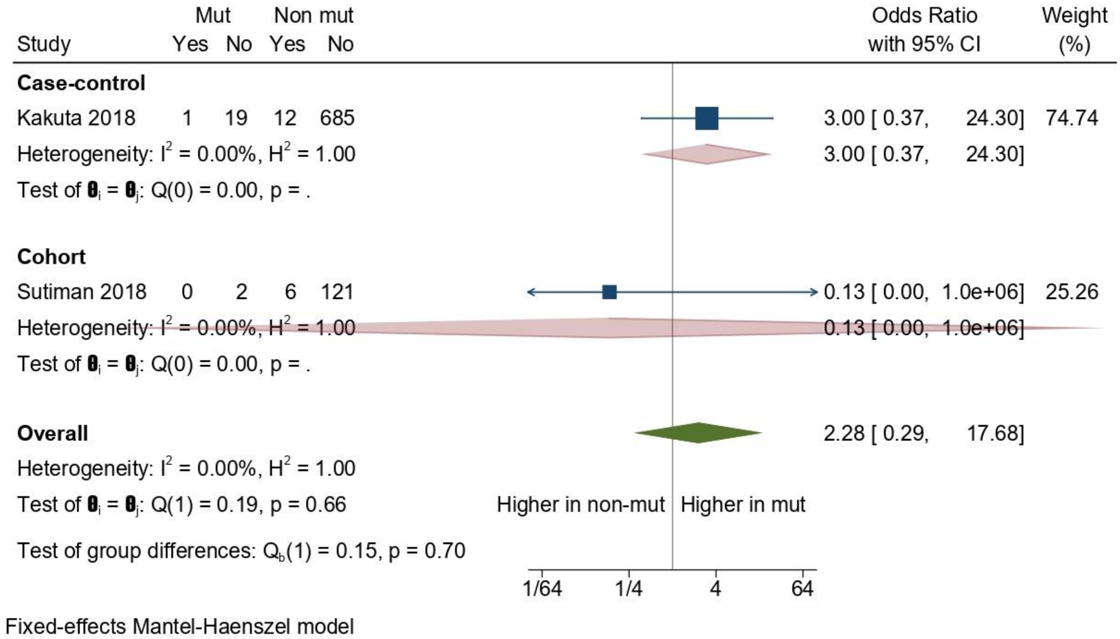


Figure S218. Forest plot of comparison *NUDT155 vs wild-type, outcome: Serious hematologic adverse events**

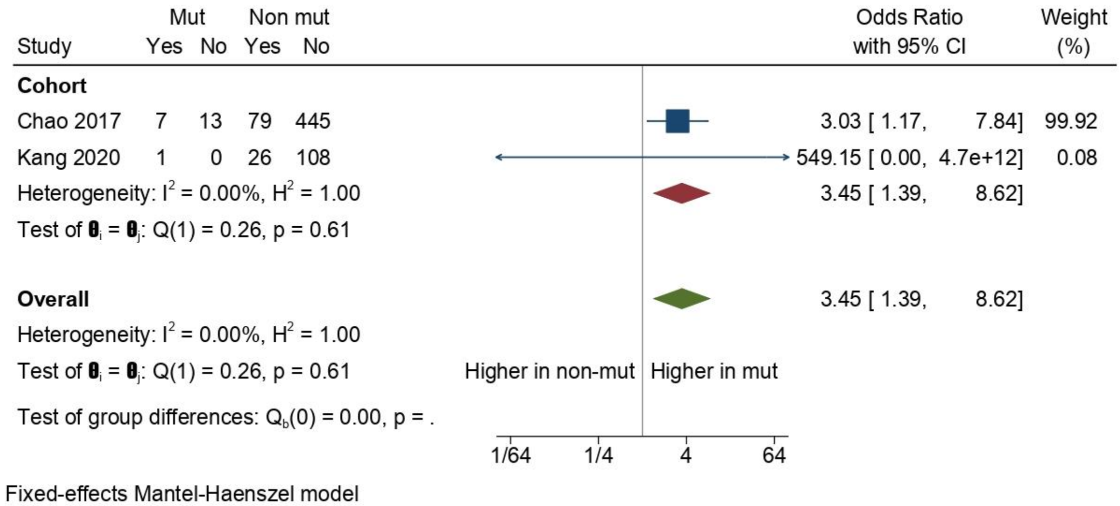


Figure S219. Forest plot of comparison *NUDT156 heterozygous vs wild-type, outcome: Total hematologic adverse events**

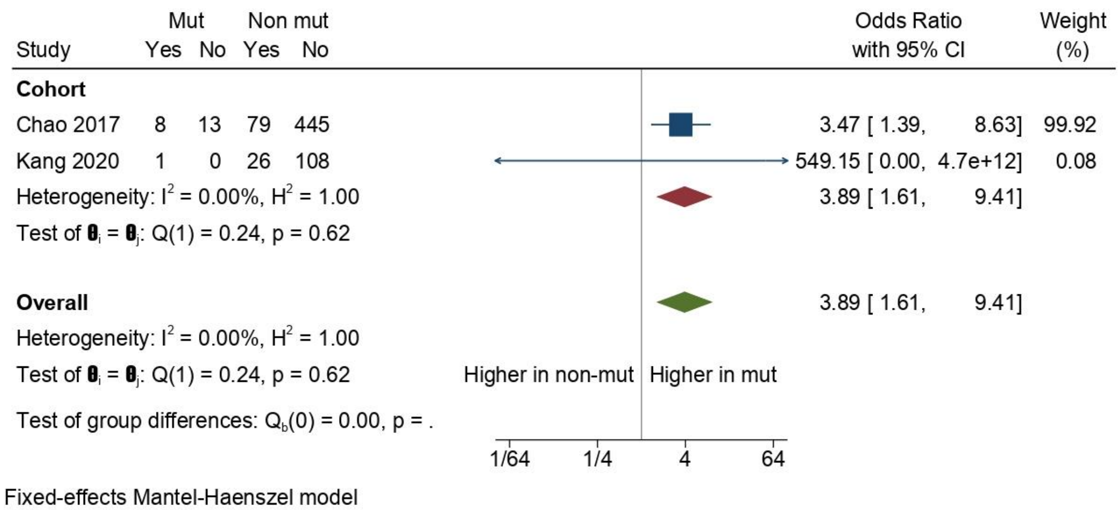


Figure S220. Forest plot of comparison *NUDT156 vs wild-type, outcome: Total hematologic adverse events**

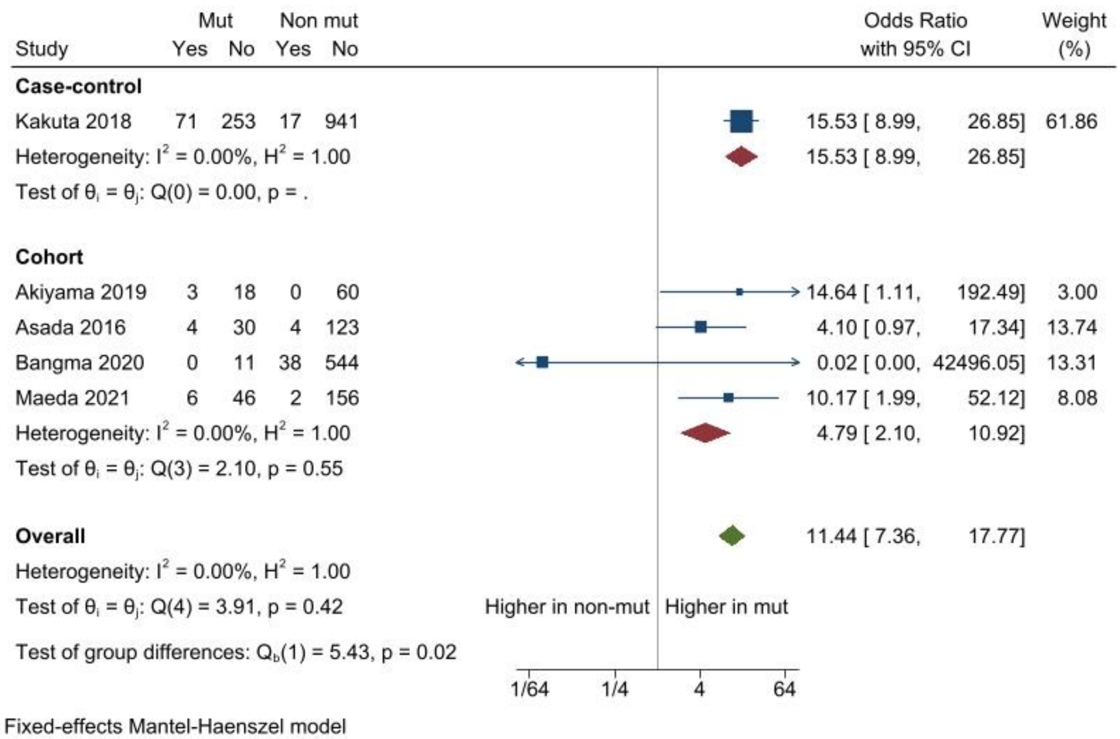


Figure S221. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Total SAE

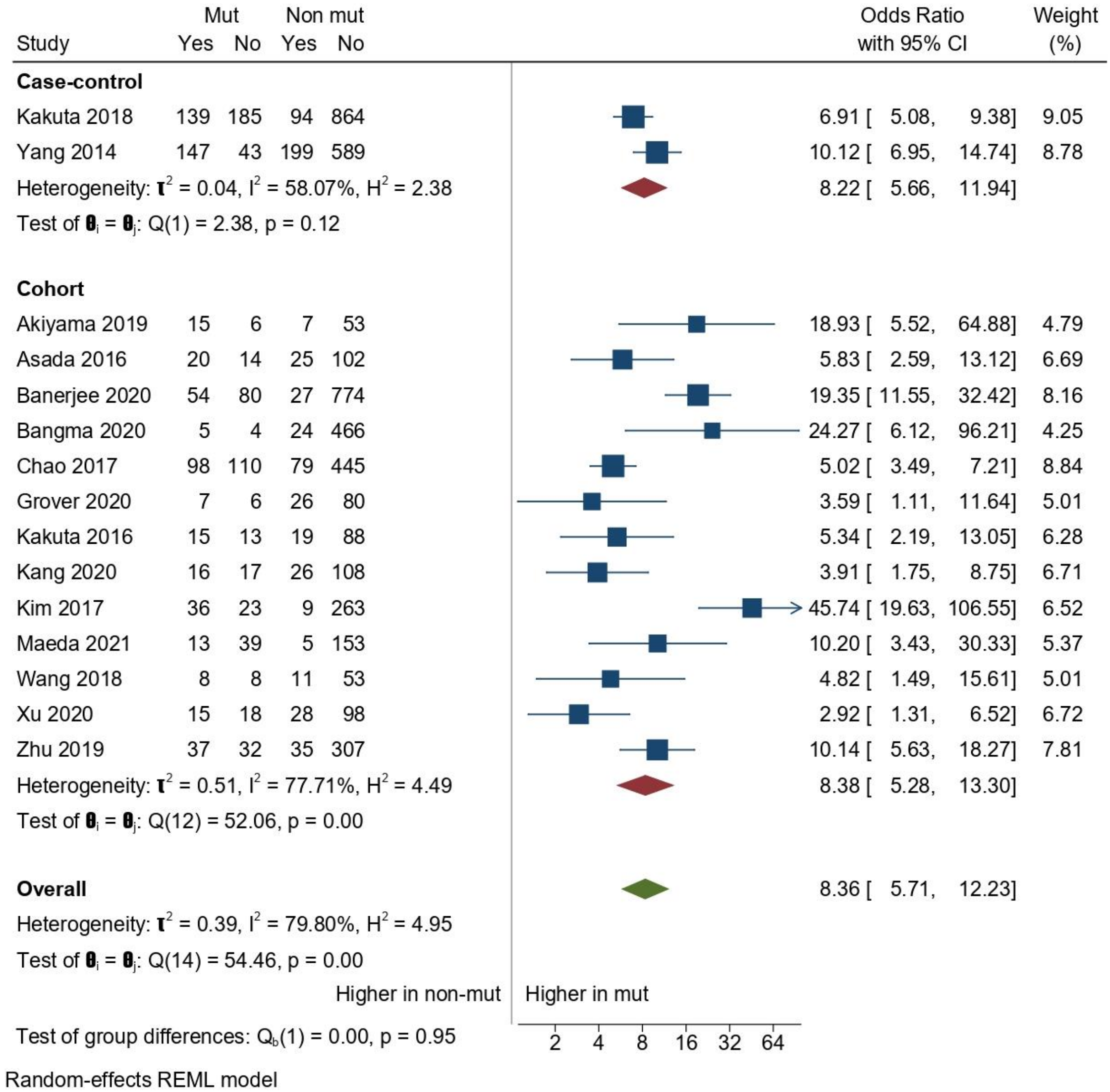


Figure S222. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Total hematologic AE

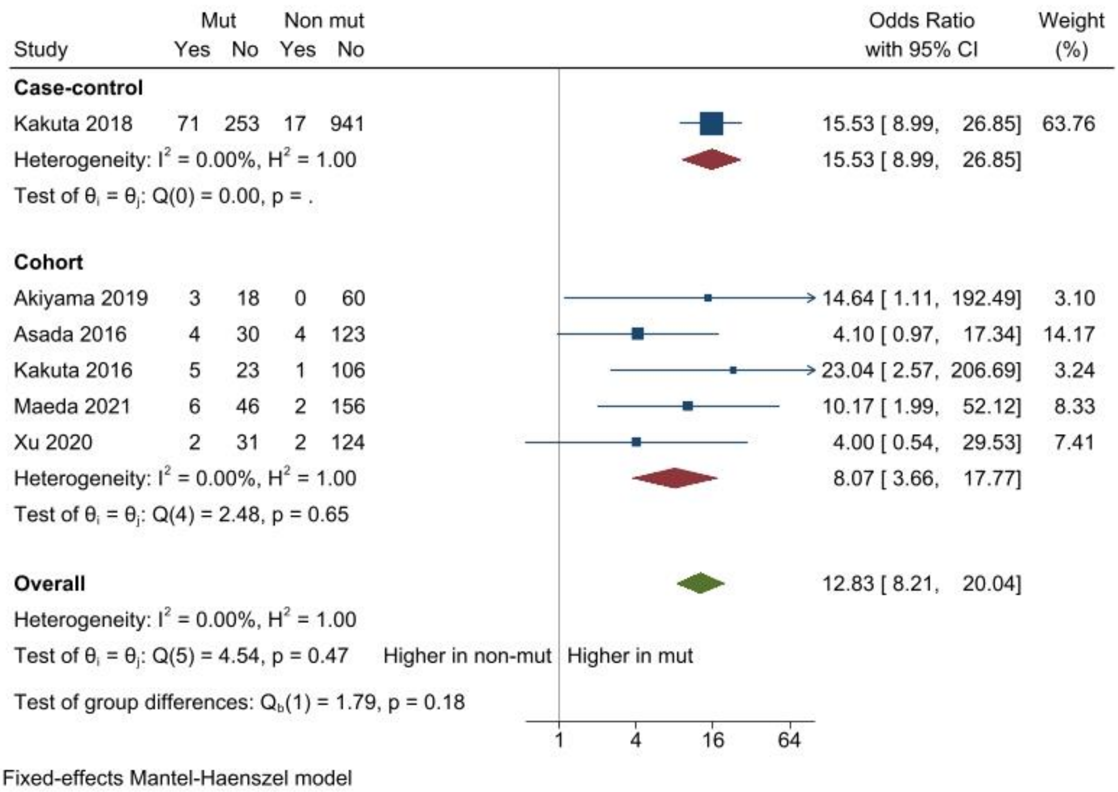


Figure S223. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Serious hematologic AE

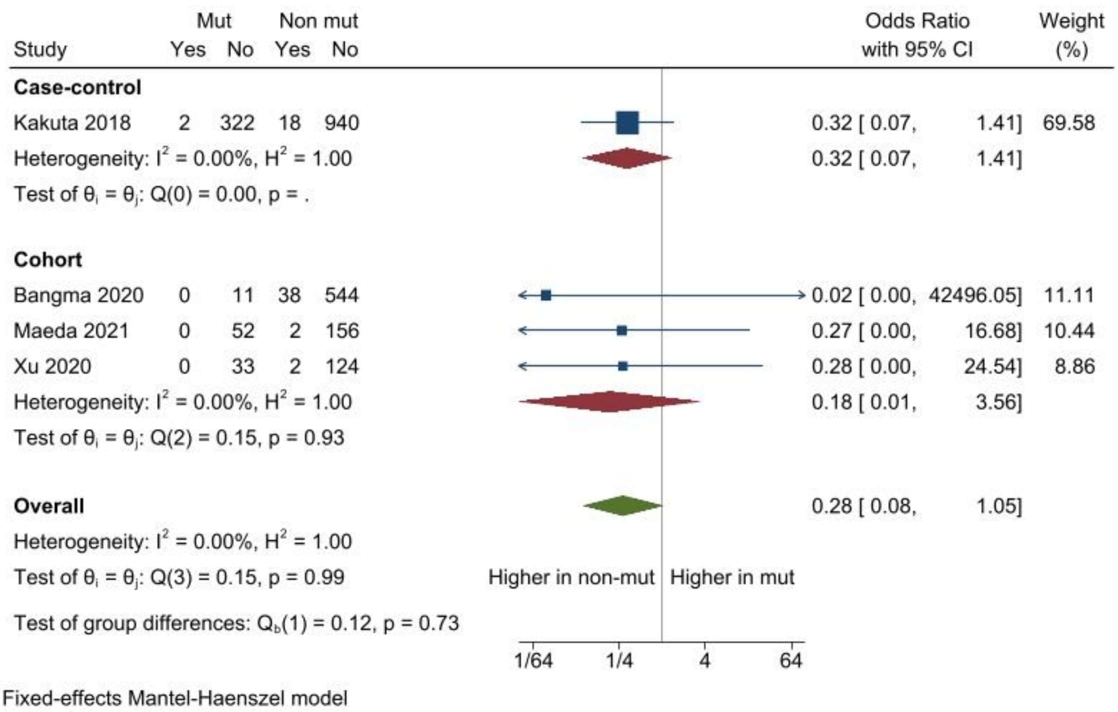


Figure S224. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Pancreatitis

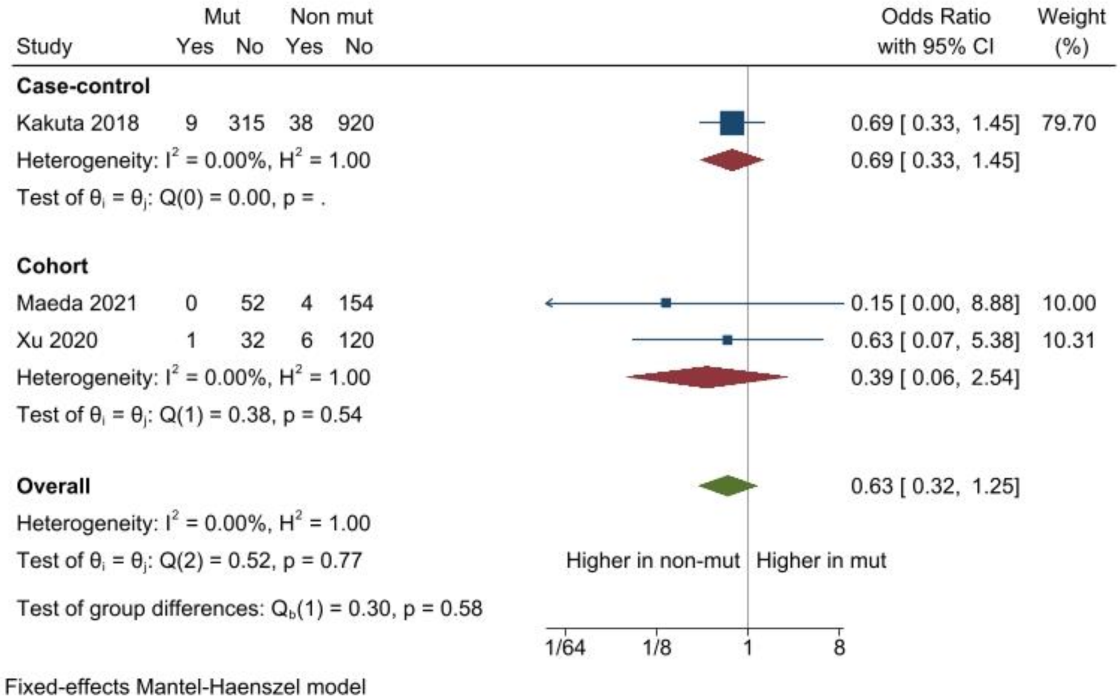


Figure S225. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Hepatotoxicity

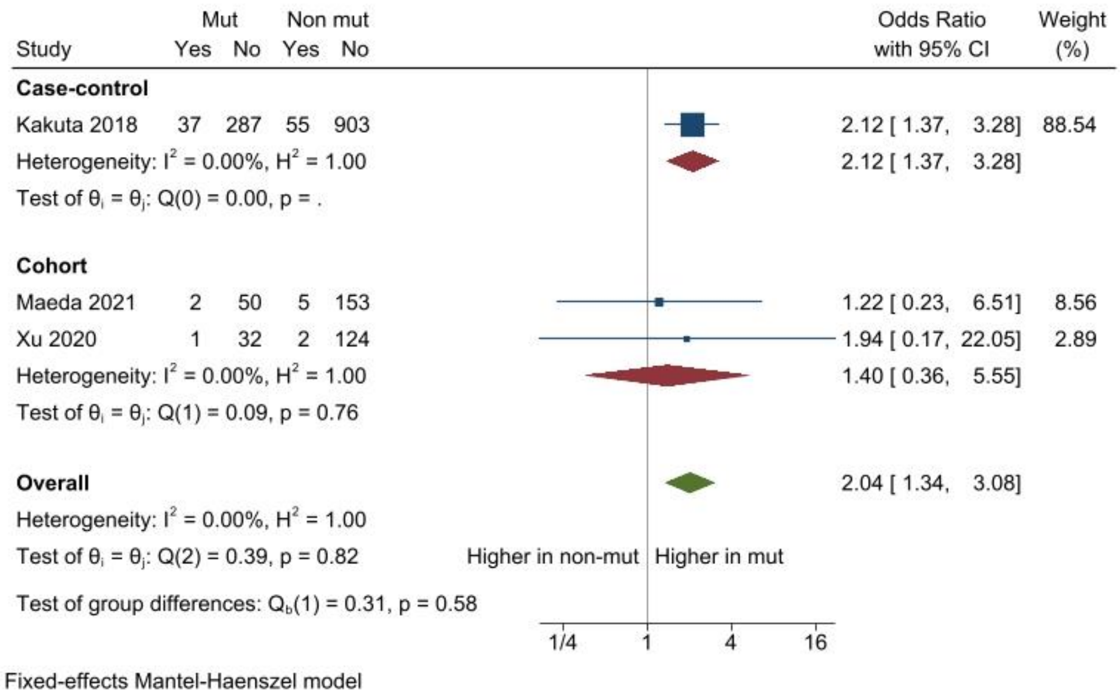


Figure S226. Sensitivity analysis excluding studies with high risk of bias. Forest plot of comparison mutated *NUDT15* vs wild-type, outcome: Gastrointestinal side effects

OTHER GENES

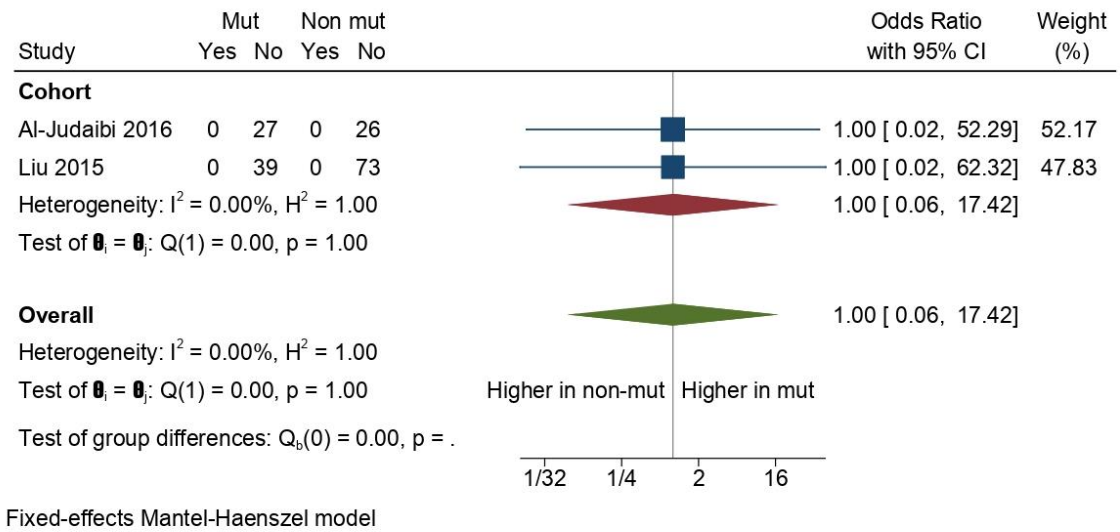


Figure S227. Forest plot of comparison mutated GSTP1 vs wild-type, outcome: Pancreatitis

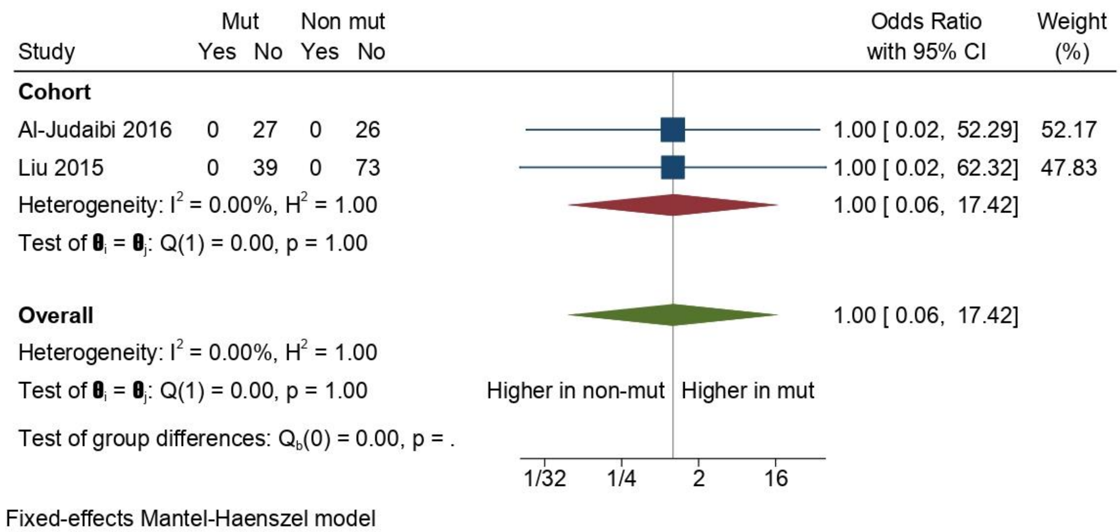


Figure S228. Forest plot of comparison mutated GSTP1 vs wild-type, outcome: Hepatotoxicity

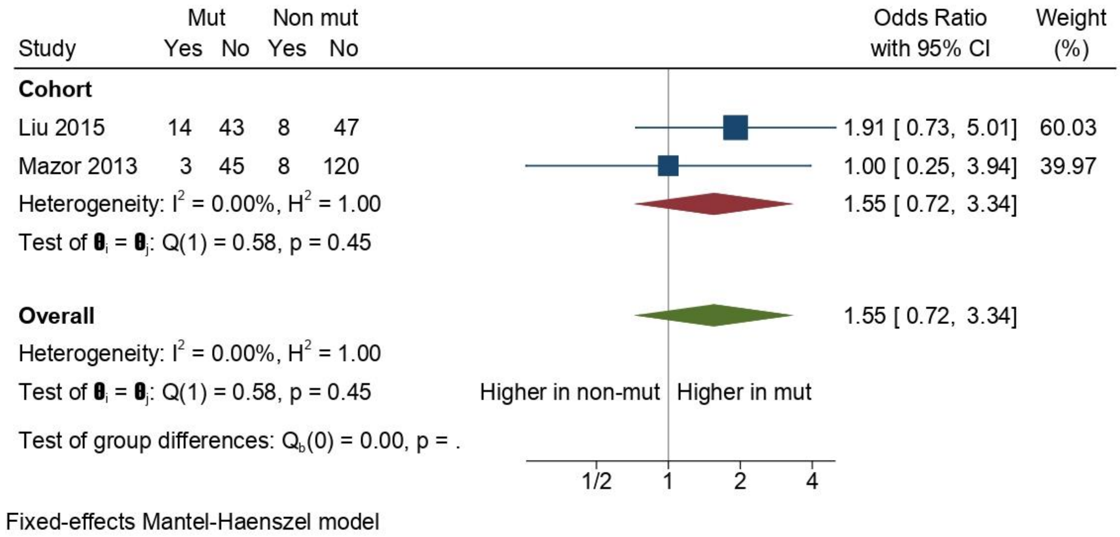


Figure S229. Forest plot of comparison mutated GSTT1 vs wild-type, outcome: Total hematologic AE

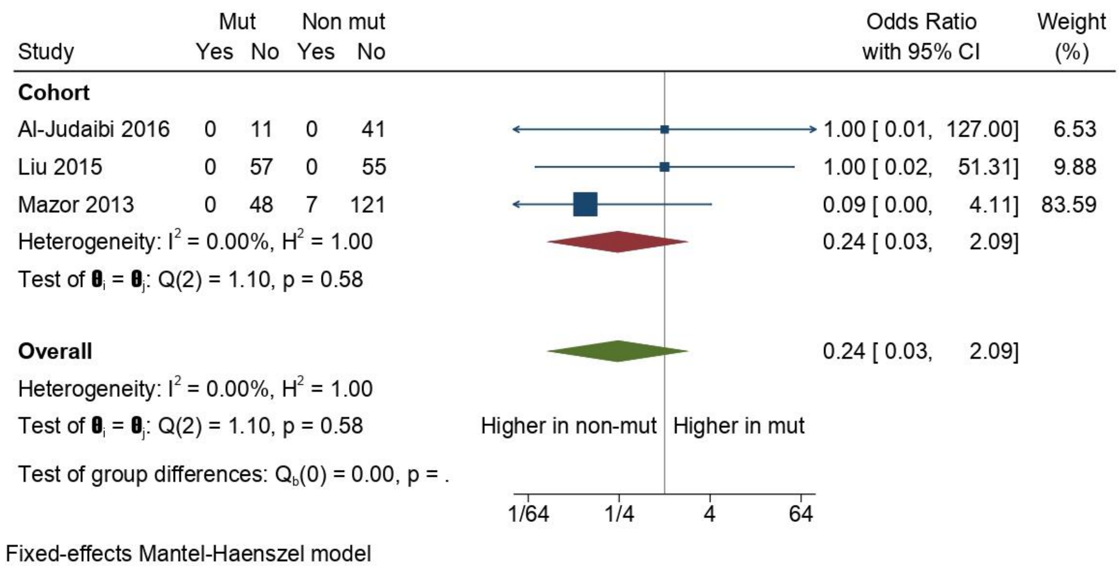


Figure S230. Forest plot of comparison mutated GSTT1 vs wild-type, outcome: Pancreatitis

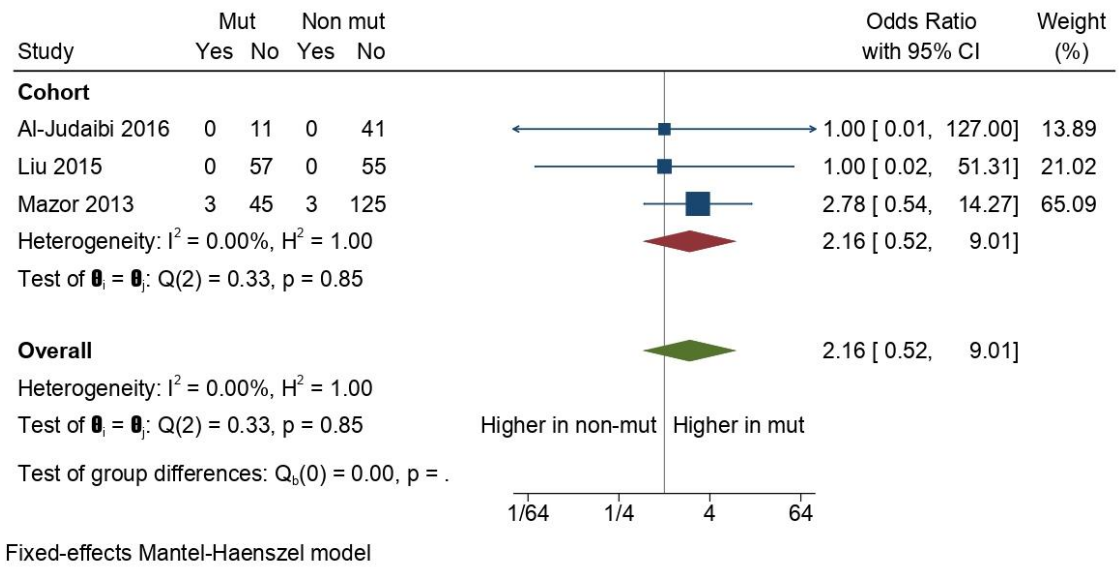


Figure S231. Forest plot of comparison mutated GSTT1 vs wild-type, outcome: Hepatotoxicity

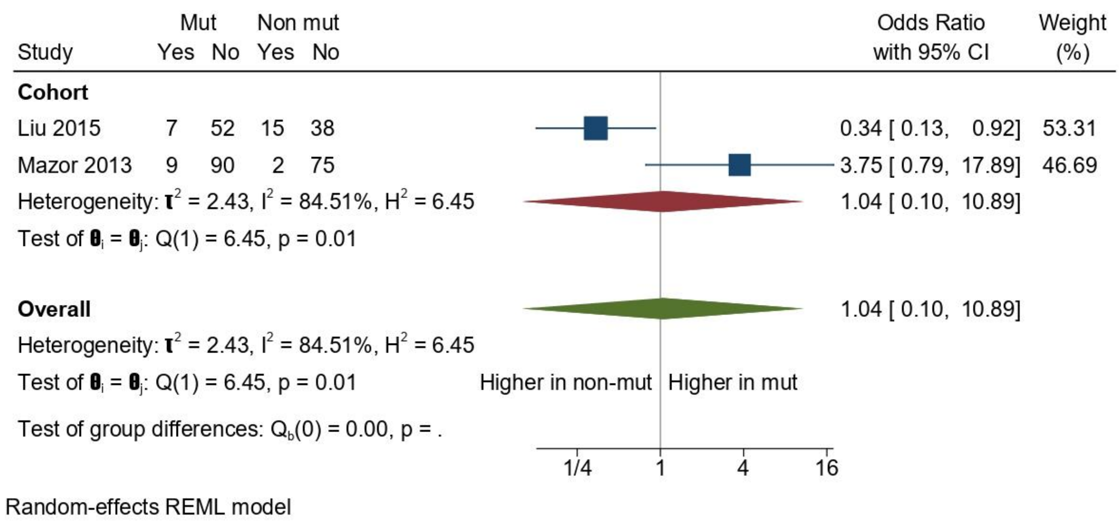


Figure S232. Forest plot of comparison mutated GSTM1 vs wild-type, outcome: Total hematologic AE

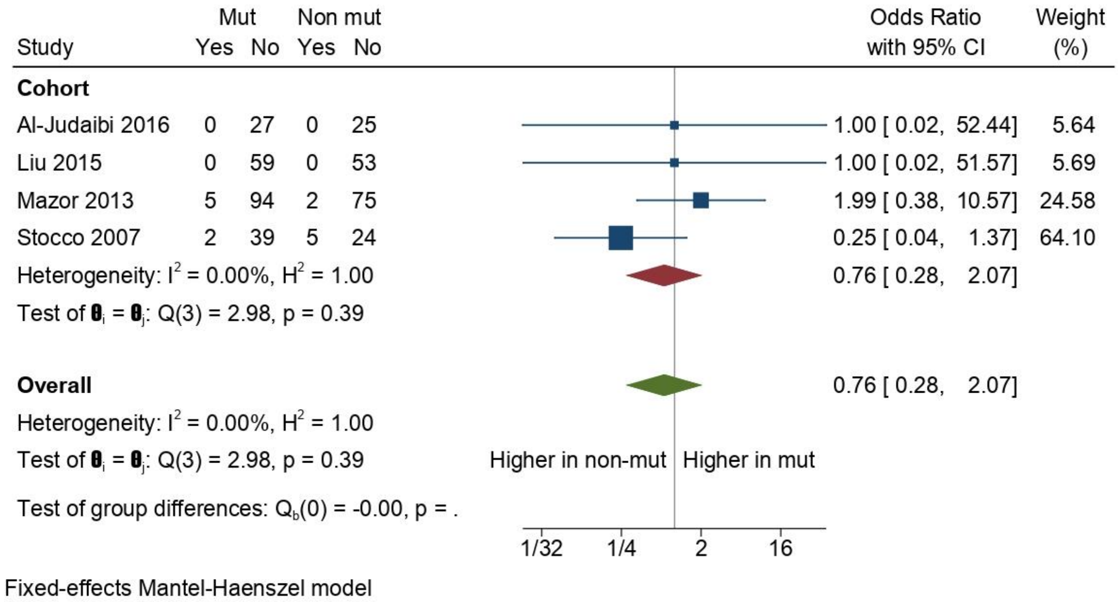


Figure S233. Forest plot of comparison mutated GSTM1 vs wild-type, outcome: Pancreatitis

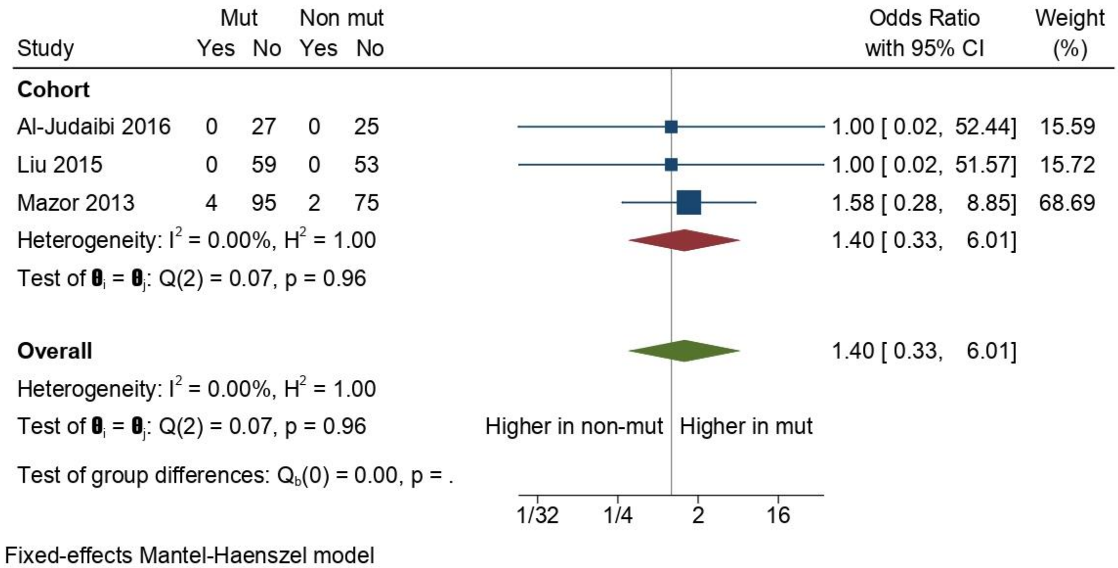


Figure S234. Forest plot of comparison mutated GSTM1 vs wild-type, outcome: Hepatotoxicity

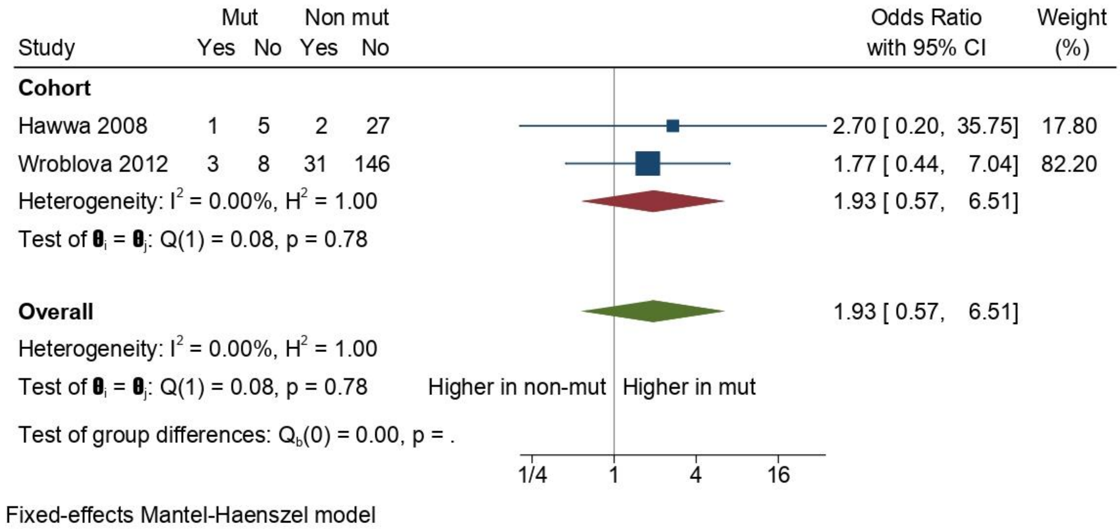


Figure S235. Forest plot of comparison XDH heterozygous vs wild-type, outcome: Total hematologic AE

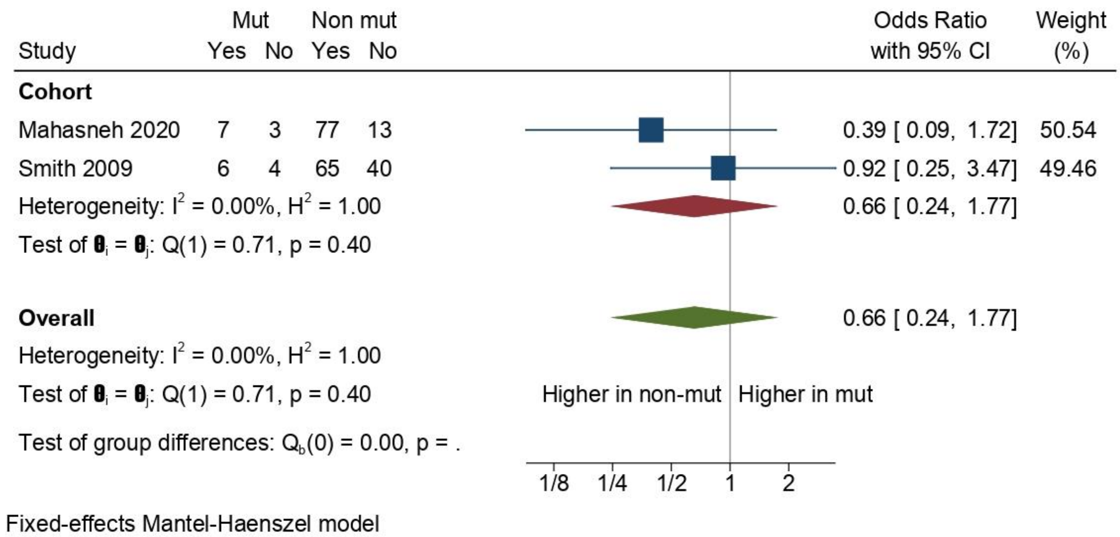


Figure S236. Forest plot of comparison mutated XDH rs17323225 vs wild-type, outcome: Clinical remission

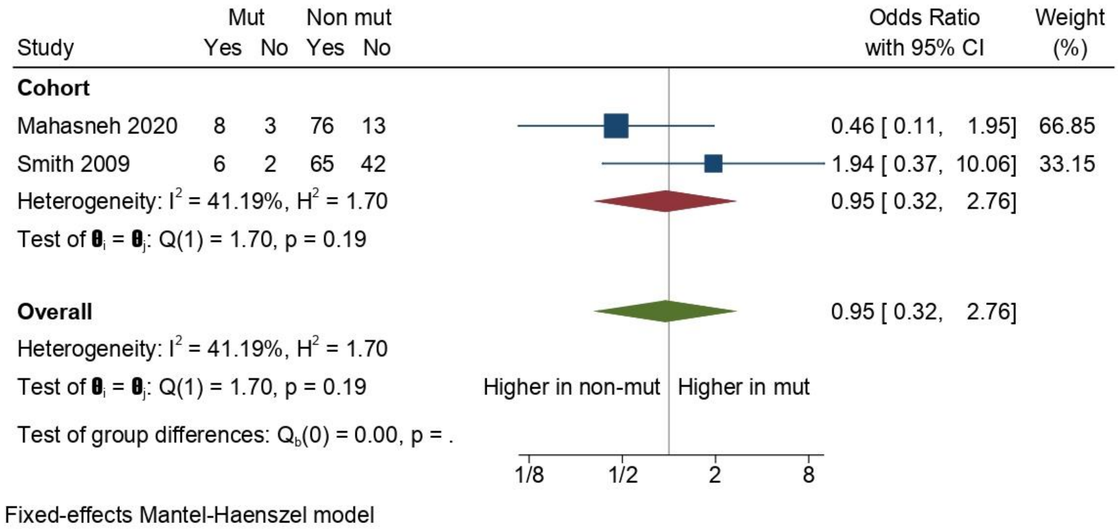


Figure S237. Forest plot of comparison mutated XDH rs17011368 vs wild-type, outcome: Clinical remission

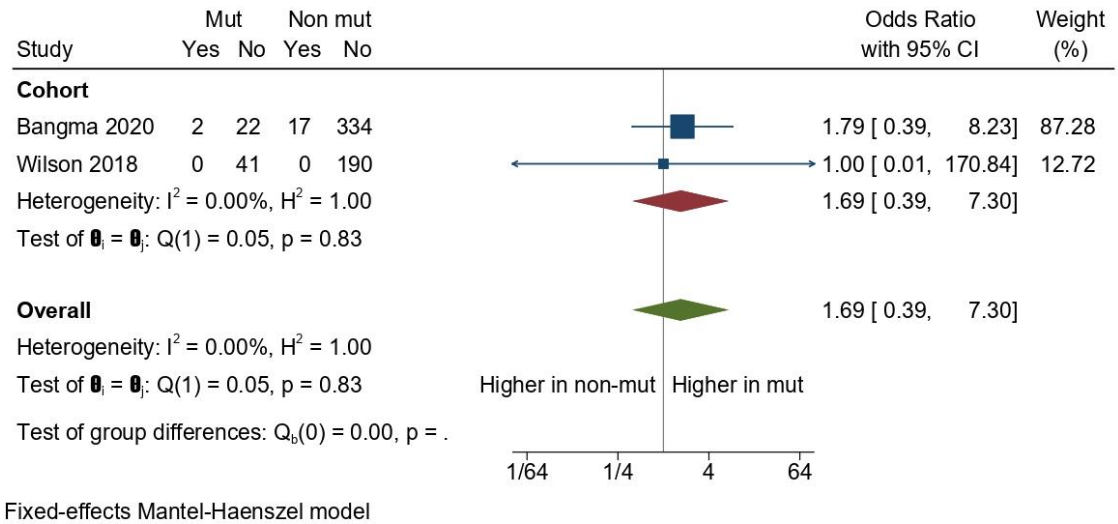


Figure S238. Forest plot of comparison HLADQA1*02:01-HLA-DRB1*07-01 rs2647087 2 mutant alleles vs wild-type, outcome: Total SAE

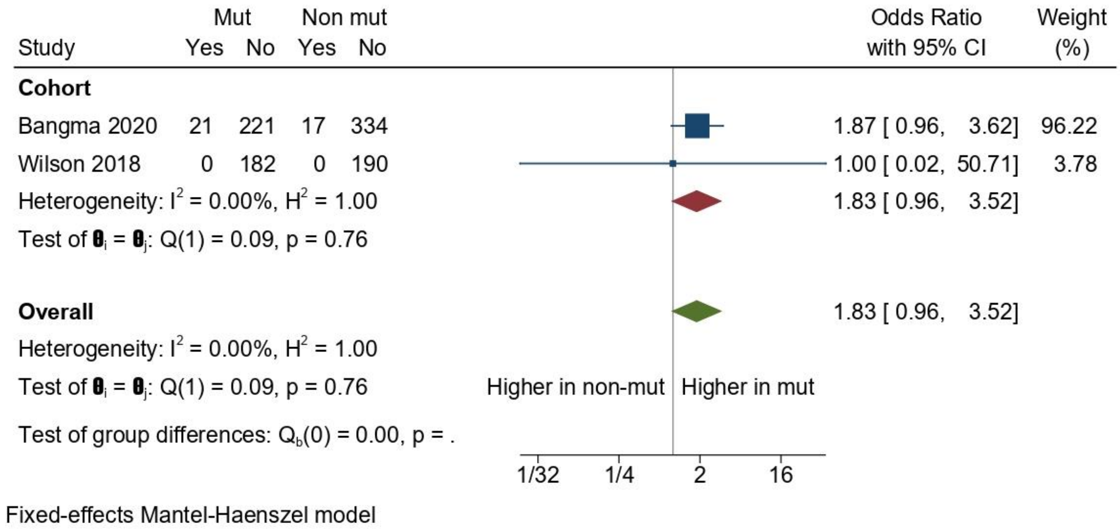


Figure S239. Forest plot of comparison mutated HLADQA1*02:01-HLA-DRB1*07-01 rs2647087 vs wild-type, outcome: Total SAE

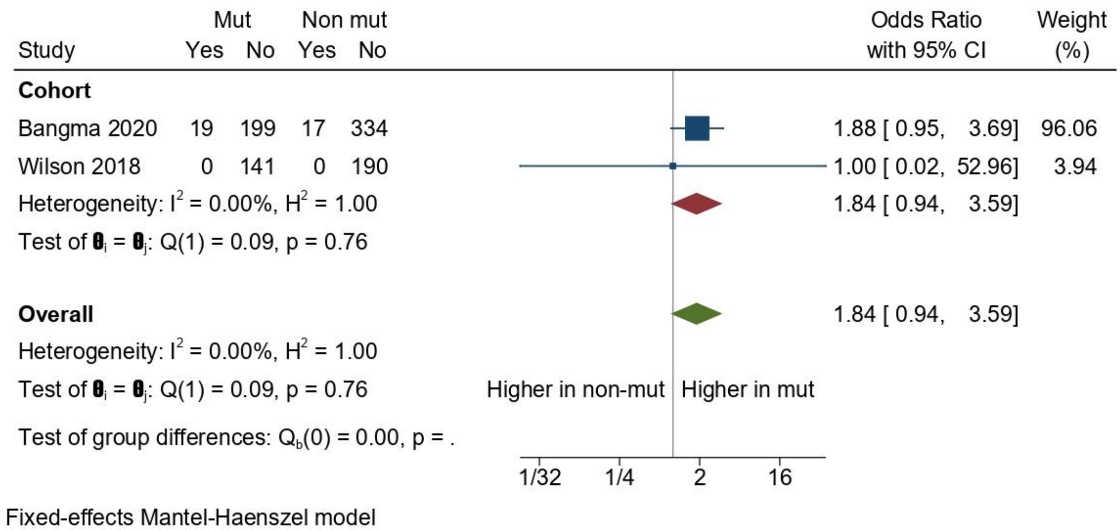


Figure S240. Forest plot of comparison HLADQA1*02:01-HLA-DRB1*07-01 rs2647087 heterozygous vs wild-type, outcome: Total serious AE

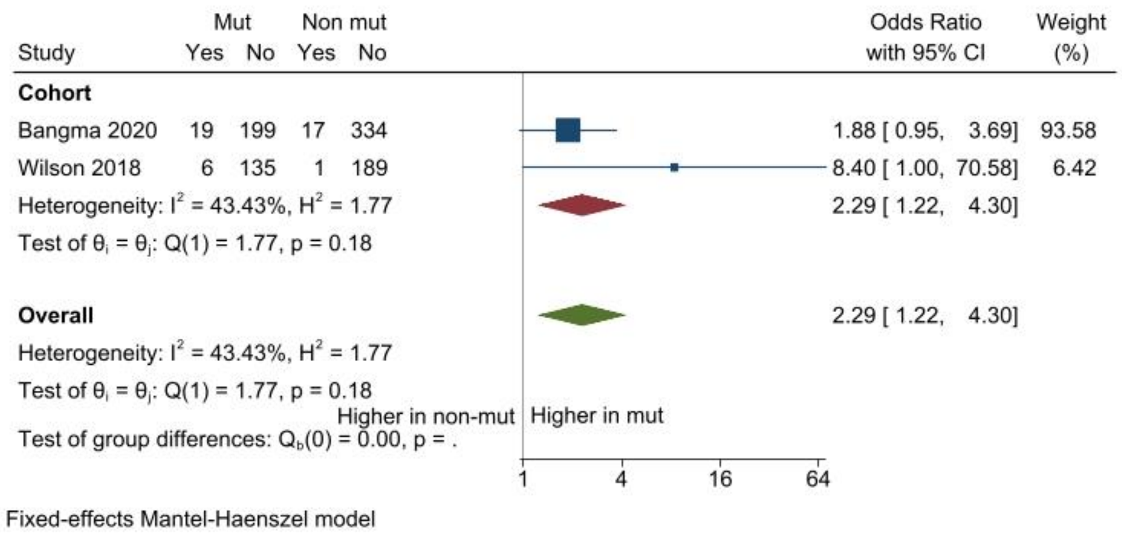


Figure S241. Forest plot of comparison HLADQA1*02:01-HLA-DRB1*07-01 rs2647087 heterozygous vs wild-type, outcome: Pancreatitis

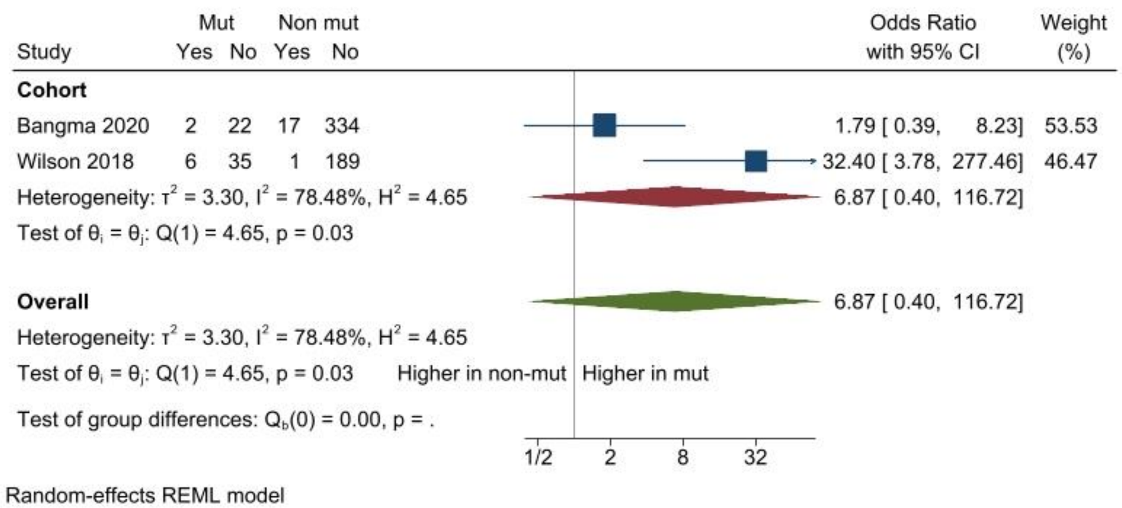


Figure S242. Forest plot of comparison HLADQA1*02:01-HLA-DRB1*07-01 rs2647087 2 mutant alleles vs wild-type, outcome: Pancreatitis

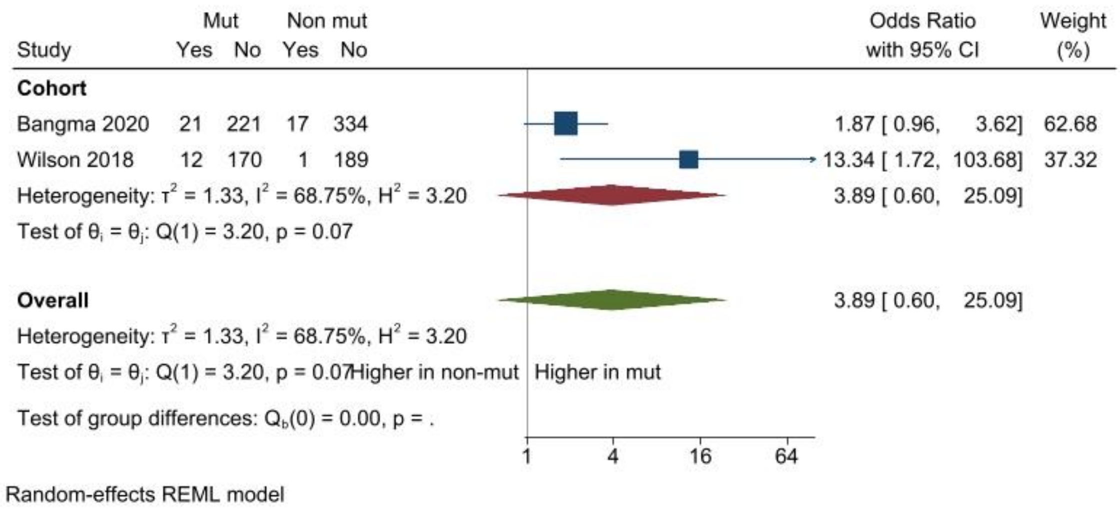


Figure S243. Forest plot of comparison mutated HLADQA1*02:01-HLA-DRB1*07-01 rs2647087 vs wild-type, outcome: Pancreatitis

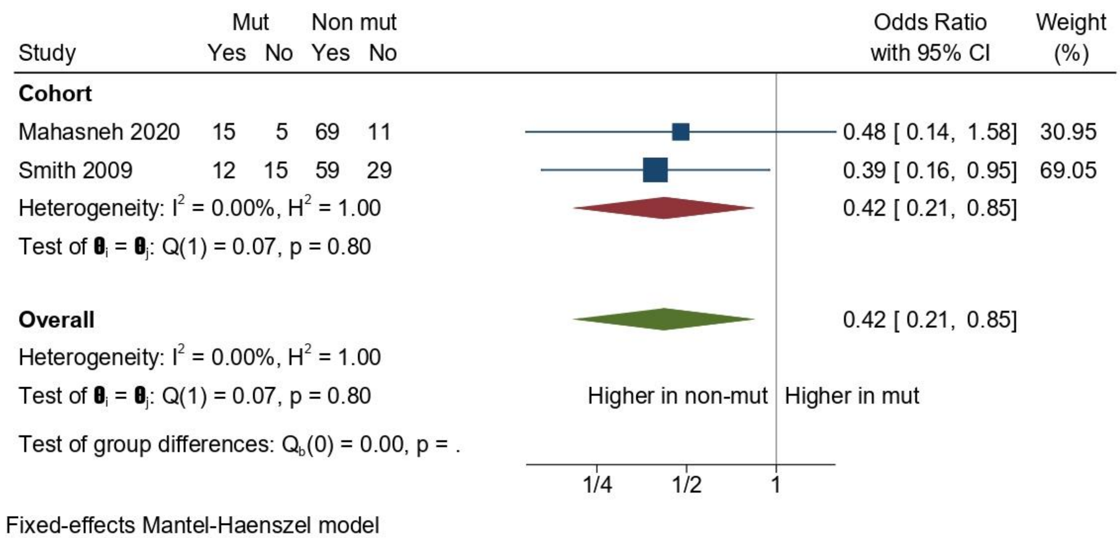


Figure S244. Forest plot of comparison mutated AOX1 rs55754655 vs wild-type, outcome: Clinical remission

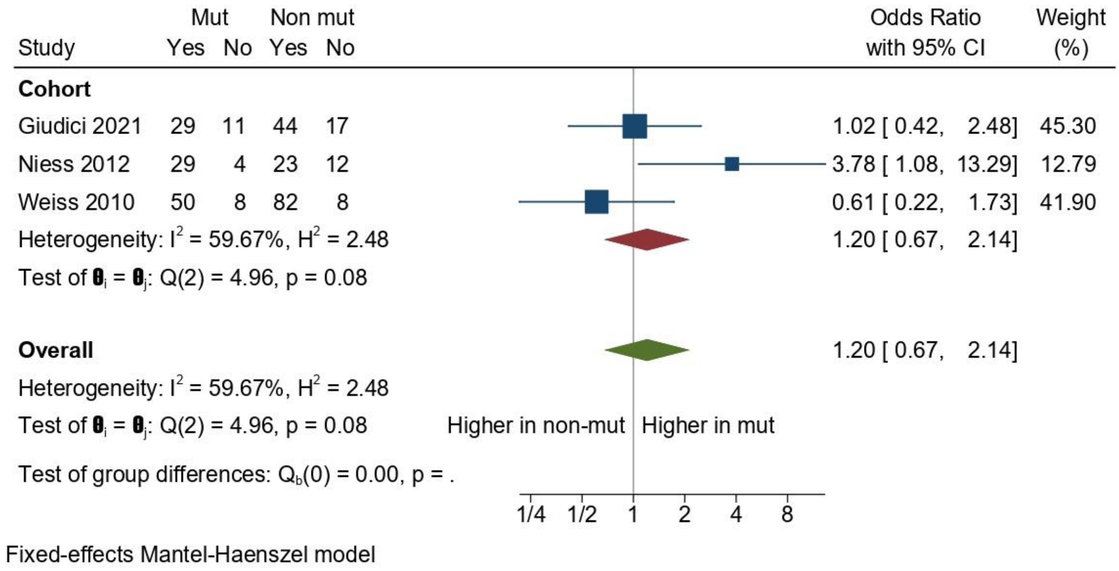


Figure S245. Forest plot of comparison mutated NOD2 vs wild-type, outcome: Clinical remission

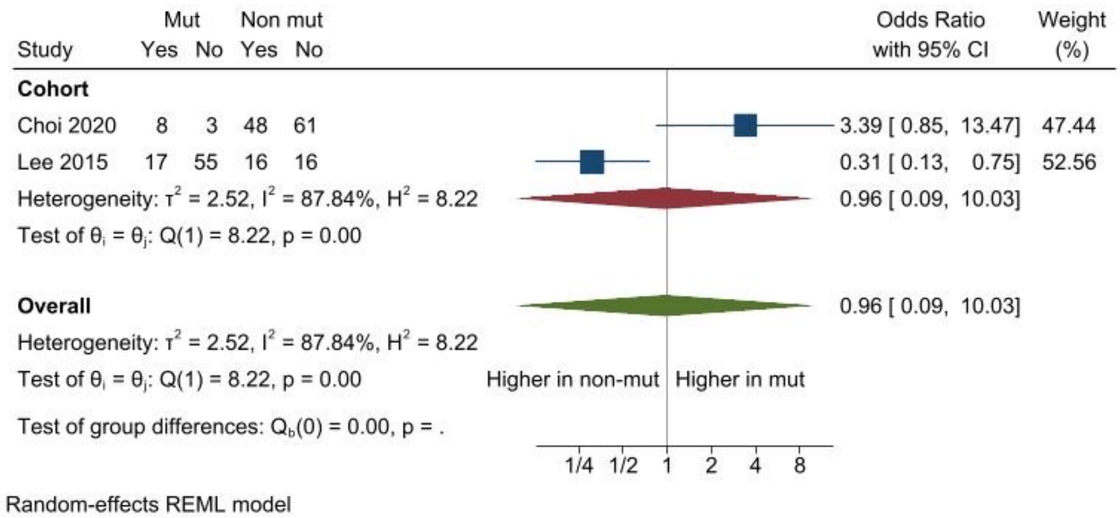


Figure S246. Forest plot of comparison IMPDH1 heterozygous vs wild-type, outcome: Total hematologic AE

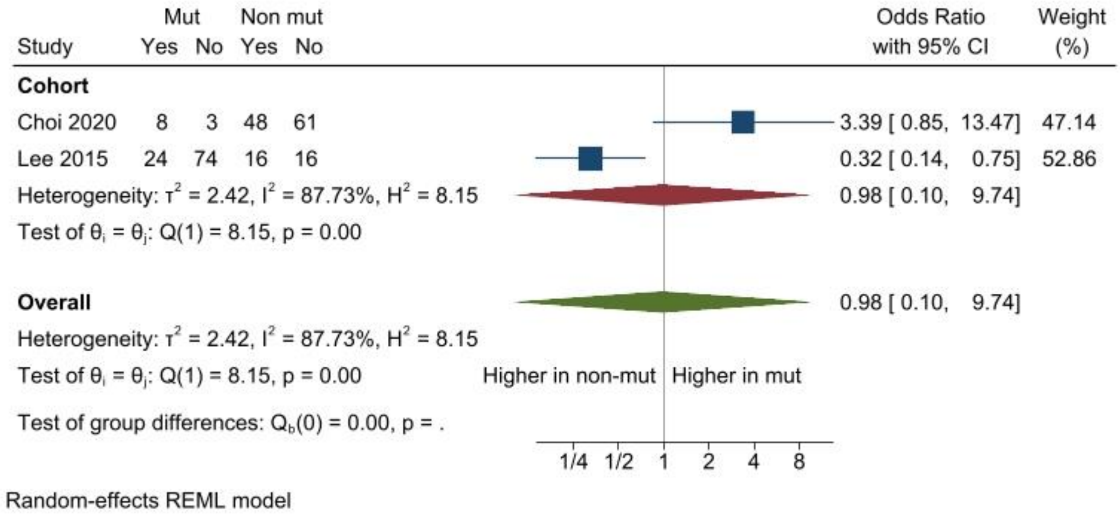


Figure S247. Forest plot of comparison mutated IMPDH1 vs wild-type, outcome: Total hematologic AE

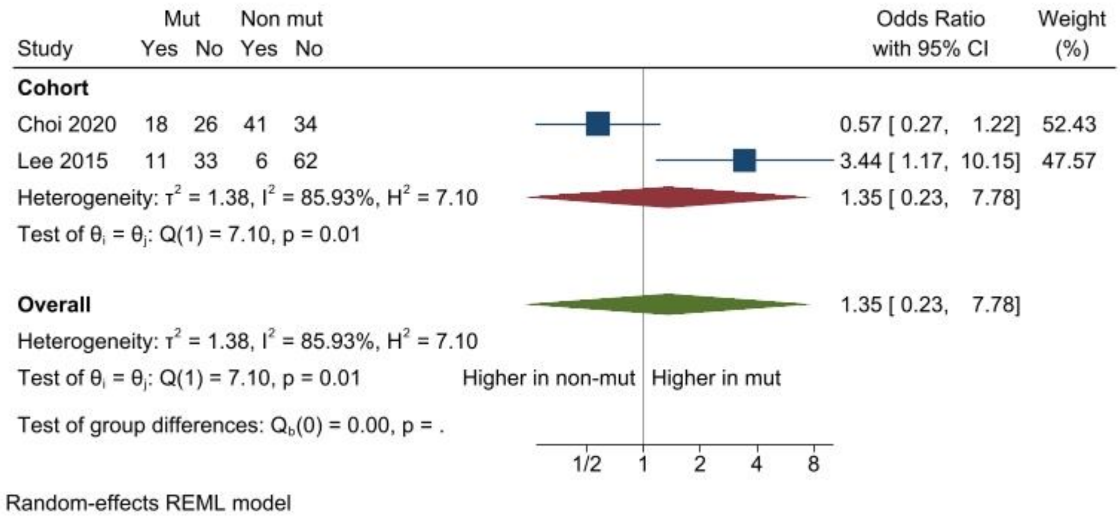


Figure S248. Forest plot of comparison SLC29A1 heterozygous vs wild-type, outcome: Total hematologic AE

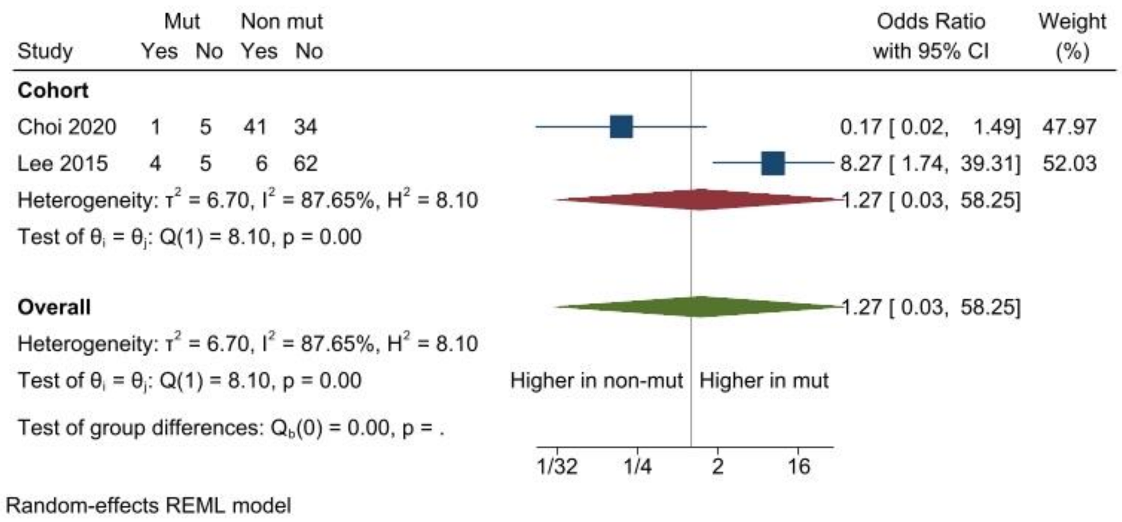


Figure S249. Forest plot of comparison SLC29A1 2 mutant alleles vs wild-type, outcome: Total hematologic AE

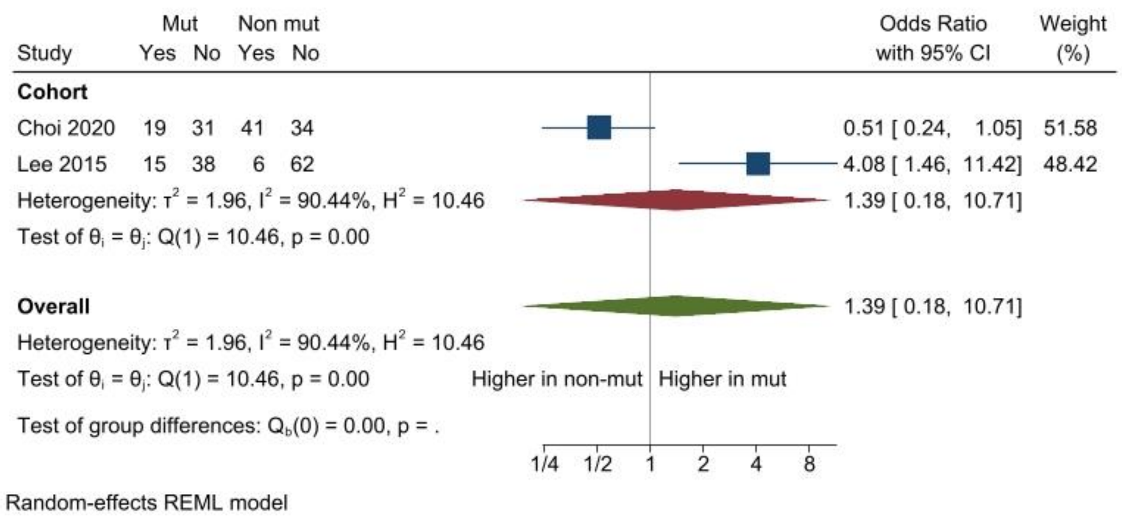


Figure S250. Forest plot of comparison mutated SLC29A1 vs wild-type, outcome: Total hematologic AE