Supplemental Information

Methods

LPS model

Age-matched male NCD-fed *Trem2*$^{-/-}$ mice and littermate wild-type (WT) mice were intraperitoneally injected with LPS (10mg/kg; MilliporeSigma, L2630). For survival experiments, mice were observed for mortality every 8 h. In some experiments, mice were sacrificed at 12 h post-LPS injection, and then blood and organs were harvested.

Cytokines test

Whole blood was collected via cardiac puncture under general anesthesia and transferred to EDTA anti-coagulant tubes. Plasma cytokines were tested either by ELISA (mouse IL-6, Invitrogen, BMS603; mouse IL-1β, Invitrogen, BMS6002; mouse TNF-α, R&D system, MTA00B) or by mouse inflammation Kit (BD, 552364).

Bacterial load measurement

Blood was collected at 24 h post-CLP. Whole blood samples obtained via cardiac puncture were serially diluted 10-fold with sterile phosphate-buffered saline (PBS). All diluted samples were inoculated on tryptic soy agar plates, and incubated at 37°C. Colony-Forming Units (CFU) were counted after 16 h incubation and results were expressed as CFU per milliliter fluid.

Histopathological Analysis

Formalin-fixed paraffin-embedded liver sections (4 μm) were stained by hematoxylin and eosin (H&E) to visualize the pattern of lipid accumulation and the inflammatory

status of the livers and lungs. NAFLD activity score referring to the published guideline was based on the degree of ballooning and lobular inflammation as follows (1, 2). Ballooning score: none = 0, few ballooned cells = 1, many ballooned cells = 2. Lobular inflammation: none foci = 0, <2 foci per 200×field = 1, 2-4 foci per 200×field = 2, >4 foci per 200×field = 3. Hepatocytes features indicating the severity of steatosis in NALFD, including macrovesicular fat or ballooned cells, were calculated to by ImageJ software in high magnification field (HMF). Liver injury score was based on severity of bleeding and infiltration as follows (3). Hemorrhages: normal = 0, mild (<30% of focal areas) = 1, moderate (30%−50% of focal areas) = 2, and severe (>50% of focal areas). = 3. Infiltration: normal = 0, mild (2−3-fold inflammatory cells) = 1, moderate (3−10-fold of inflammatory cells) = 2, and severe (>10-fold inflammatory cells) = 3. Lung injury was scored from 1 (normal) to 5 (severe) as described previously (4). Histopathological evaluation was determined in 5-6 fields per section by obtaining its mean value to avoid contingency and conducted by two examiners without prior knowledge on the experimental procedures. Oil Red O (ORO) (Sangon Biotech, A600395-0050) staining was used to assess the lipid droplet accumulation in liver by using frozen liver sections (10 μm) (5). Histopathology images were acquired with a light microscope (Olympus).

***Oil red O (ORO) staining of hepatocytes* in vitro**

ORO staining of hepatocytes was performed as published (5). Cells were fixed with 4% neutral formaldehyde for 10 min then washed by PBS three times, followed by incubation with ORO dilution (original liquid: distilled deionized water = 3:2, filtered

before use) for 20 min. Then cells were washed by isopropanol dilution (isopropanol: dd water = 3:2), and kept in PBS for observation by light microscope (Olympus).

Immunostaining

Immunofluorescence was performed on 10 μm frozen sections from isolated livers. Sections were fixed with methylalcohol and permeabilized with 0.25% Triton X-100 and blocked with 3% BSA in PBS, and then stained with antibodies for 24 or 48 h at 4 °C: anti-human TREM2 (21E10, mouse monoclonal, 20ug/ml; expressed by our own lab) (6), anti-human CD68 (KP1, mouse monoclonal, 1:100; Thermo Fisher Scientific, MA5-13324) for DCD liver samples; anti-mouse *Trem2* (178, mouse monoclonal, 20ug/ml; produced by our lab) (7), anti-mouse F4/80 (BM8.1, rat monoclonal, 1:100; Cell signaling technology, 71299) for NCD/HFD-fed mice liver samples; anti-human TREM2 (D8I4C, rabbit monoclonal, 1:100; Cell signaling technology, 91068), anti-mouse Iba1 (E4O4W, rabbit monoclonal, 1:100; Cell signaling technology, 17198) for HFD-fed BAC transgenic mice. After washing with PBST (PBS containing 0.025% tween 20) for three times, sections were stained with goat anti-mouse IgG2a, Alexa Fluor 594 (1:500; Invitrogen, A-21135); goat anti-rabbit IgG, Alexa Fluor 555 (1:500; Abcam, ab150074); goat anti-mouse IgG, Alexa Fluor 488 (1:500; Invitrogen, A-10680) or goat anti-rat IgG, Alexa Fluor 647 (1:500; Invitrogen, A-21247) for 1 h at room temperature. All antibodies were diluted in blocking buffer. Nikon A1R confocal microscope was used to collect images.

Bone marrow derived macrophages

Bone marrow derived macrophages (BMDMs) were prepared according to a

published protocol (8). Briefly, femurs and tibias were removed and flushed with sterile PBS. Red blood cells were lysed by lysis buffer (eBioscience, 00-4333-57) for 2 mins and cells were washed once by sterile PBS. Bone marrow cells were counted and plated in 75-cm^2 flask in DMEM supplement with 10% FBS and 1% penicillin–streptomycin (P/S) and 20 ng/ml mouse granulocyte macrophage-colony stimulating factor (GM-CSF; PeproTech, 315-03). Twenty-four hours later, nonadherent cells were collected and replanted with a density of 10^7 cells per 75-cm^2 flasks. The cells were incubated for 6~7 days with medium exchange every 3 days.

Cell lines

BNL.CL2 cell line was purchased from the Cell Bank of Type Culture Collection of Chinese Academy of Sciences, Shanghai, China. Cells were cultured in standard medium comprising Dulbecco's modified Eagle's medium (DMEM; Gibco, C11995500BT) supplemented with10% FBS (Gibco, 10099-141) and 1% P/S (Gibco, 15140-122) at 37°C in an incubator with 5% CO_2.

Liver function assay

Liver functions were evaluated by determining the plasma concentrations of albumin, Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) using assay kits (Nanjing Jiancheng Bioengineering Institute, A028-2-1, C009-2-1 and C010-2-1, respectively).

Liver lipid species assay

Extraction preparation for liquid chromatography-mass spectrometry (LC-MS) analysis: The liver samples were thawed on ice, and metabolites were extracted with

50% methanol buffer. Briefly, 100 mg of each sample was extracted with 120 μl of precooled 50% methanol, vortexed for 1 min, and incubated at room temperature for 10 min; the extraction mixture was then stored overnight at -20°C . After centrifugation at 4,000 g for 20 min, the supernatants were transferred into 96-well plates and stored at -80°C prior to the LC-MS analysis. In addition, pooled quality control (QC) samples were also prepared by combining 10 μl of each extraction mixture.

LC-MS analysis: All samples were acquired by the LC-MS system. All chromatographic separations were performed using an ultra-performance liquid chromatography (UPLC) system (SCIEX). An ACQUITY UPLC T3 column (100mm X 2.1mm, 1.8μm, Waters) was used for the reversed phase separation. The column oven was maintained at 35°C. The flow rate was 0.4 ml/min, and the mobile phase consisted of solvent A (water, 0.1% formic acid) and solvent B (Acetonitrile, 0.1% formic acid). Gradient elution conditions were set as follows: 0 ~ 0.5 min, 5% B; 0.5 ~ 7 min, 5% to 100% B; 7~8 min, 100% B; 8 ~ 8.1 min, 100% to 5% B; 8.1 ~ 10 min, 5% B. The injection volume for each sample was 4 μl.

A high-resolution tandem mass spectrometer TripleTOF5600plus (SCIEX) was used to detect metabolites eluted from the column. The Q-TOF was operated in both positive and negative ion modes. The curtain gas was set 30 PSI, Ion source gas1 was set 60 PSI, Ion source gas2 was set 60 PSI, and an interface heater temperature was 650°C. For positive ion mode, the Ion spray voltage floating were set at 5000 V. For negative ion mode, the Ion spray voltage floating were set at -4500V. The mass spectrometry data were acquired in IDA mode. The TOF mass range was from 60 to

1200 Da. The survey scans were acquired in 150 ms and as many as 12 product ion scans were collected if exceeding a threshold of 100 counts per second (counts/s) and with a 1+ charge-state. Total cycle time was fixed to 0.56 s. Four time bins were summed for each scan at a pulse frequency value of 11 kHz through monitoring of the 40 GHz multichannel TDC detector with four-anode/channel detection. Dynamic exclusion was set for 4 s. During the acquisition, the mass accuracy was calibrated every 20 samples. Furthermore, in order to evaluate the stability of the LC-MS during the whole acquisition, a QC sample (pool of all samples) was acquired after every 10 samples.

Data processing and analysis: The acquired MS data pretreatments including peak picking, peak grouping, retention time (RT) correction, second peak grouping, and annotation of isotopes and adducts were performed using XCMS software. LC-MS raw data files were converted into mzXML format and then processed by the XCMS, CAMERA and metaX toolbox implemented with the R software. Each ion was identified by combining RT and m/z data. Intensities of each peak were recorded and a three dimensional matrix containing arbitrarily assigned peak indices (RT-m/z pairs), sample names (observations) and ion intensity information (variables) were generated. The online KEGG and HMDB database were used to annotate the metabolites by matching the exact molecular mass data (m/z) of samples with those from database. If a mass difference between observed and the database value was less than 10 ppm, the metabolite would be annotated and the molecular formula of metabolites would further be identified and validated by the isotopic distribution

measurements. Also, an in-house fragment spectrum library of metabolites was used to validate the metabolite identification (LC-Bio Technologies).

The intensity of peak data was further preprocessed by metaX. Those features that were detected in less than 50% of QC samples or 80% of biological samples were removed. The remaining peaks with missing values were imputed with the k-nearest neighbor algorithm to further improve the data quality. QC-based robust LOESS signal correction was fitted to the QC data with respect to the order of injection to minimize signal intensity drift over time. In addition, the relative standard deviations of the metabolic features were calculated across to all QC samples, and those > 30% were then removed. Student's *t* test was conducted to detect differences in metabolite concentrations between *Trem2*$^{-/-}$ and WT groups. The *P* value was adjusted for multiple tests using an FDR (Benjamini–Hochberg). Supervised PLS-DA was conducted through metaX to discriminate the different variables between groups. A VIP cut-off value of 1.0 was used to select important features.

Triglyceride and cholesterol assay

Liver or serum triglyceride and cholesterol were determined using Triglyceride Colorimetric Assay Kit (Cayman Chemical, 10010303) and Cholesterol Quantification Kit (MilliporeSigma, MAK043) according to manufacturer's instructions.

ATP determination

ATP levels of hepatocytes or livers were analyzed by ATP Determination Kit (Invitrogen, A22066), referring to its user's manual.

Western blot

Equal amount of proteins from exosome samples or cellular lysates were resolved in 4%-12% Bis-Tris NUPAGE gradient gels with MOPS running buffer. Proteins were transferred onto polyvinylidene difluoride membranes and blotted with following indicated antibodies: anti-CD63 (MX-49.129.5, mouse monoclonal, 1:1000; Santa Cruz Biotechnology, sc-5275), anti-CD81 (B-11, mouse monoclonal, 1:1000; Santa Cruz Biotechnology, sc-166029), anti-Alix (1A12, mouse monoclonal, 1:1000; Santa Cruz Biotechnology, sc-53540), anti-cytochrome-C (EPR1327, rabbit monoclonal, 1:1000; Abcam, ab133504) or anti-GM130 (EP892Y, rabbit monoclonal, 1:1000; Abcam, ab52649), anti-calnexin (EPR3633(2), rabbit monoclonal, 1:1000; Abcam, ab133615) and anti-Mfn2 (D2D10, rabbit monoclonal, 1:1000; Cell Signaling Technology, 9482) overnight at 4°C. All antibodies were diluted in 5% BSA/PBS. Membranes were then incubated with corresponding secondary antibodies for 1 h at room temperature. Western blots were developed by enhanced chemiluminescence (Biological Industries, 20-500-120) and detected by X-ray films. The resulting protein bands were analyzed with ImageJ Analyzer.

Reference:

1. Takahashi Y, Fukusato T. Histopathology of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *World J Gastroenterol.* 2014;20(42):15539-15548.
2. Harrison SA, et al. NGM282 for treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet.* 2018;391(10126):1174-1185.
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4. Hou JC, Sphingosine 1-phosphate receptor 2 signaling suppresses macrophage phagocytosis and impairs host defense against sepsis. *Anesthesiology.* 2015;123(2):409-422.
5. Luo XJ, et al. Expression of STING is increased in liver tissues from patients with NAFLD and promotes macrophage-mediated hepatic inflammation and fibrosis in mice. *Gastroenterology.* 2018;155(6):1971-1984.
6. Cella M, Buonsanti C, Strader C, Kondo T, Salmaggi A, Colonna M. Impaired differentiation of osteoclasts in TREM-2-deficient individuals. *J Exp Med.* 2003;198(4):645-651.
7. Molgora M, et al. TREM2 modulation remodels the tumor myeloid landscape enhancing anti-PD-1 immunotherapy. *Cell.* 2020;182(4):886-900.
8. Hou JC, et al. S1PR3 signaling drives bacterial killing and is required for

survival in bacterial sepsis. *Am J Respir Crit Care Med.* 2017;196(12):1559-1570.

Supplemental Figures

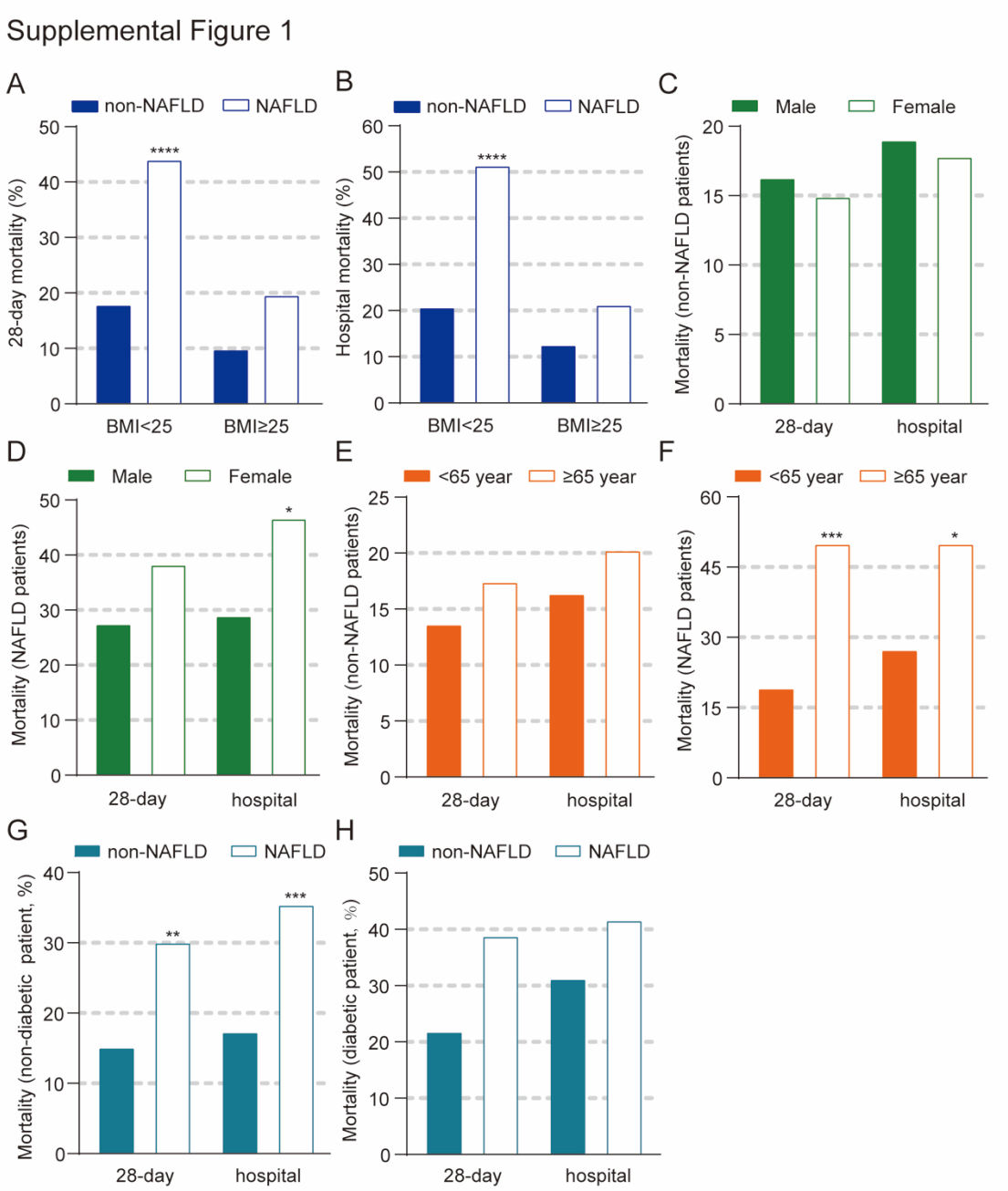

Fig. S1. NAFLD is an independent risk factor for hospital mortality in critically ill patients with sepsis. 28-day **(A)** and hospital mortality **(B)** across NAFLD and BMI categories. Significant difference compared with the non-NAFLD control was determined. *n* = 395 in non-NAFLD group, *n* = 129 in NAFLD group. **(C** and **D)** 28-day and hospital mortality in male and female patients with or without NAFLD. Significant difference compared with the male was determined. *n* = 395 in non-NAFLD group, *n* = 129 in NAFLD group. **(E** and **F)** 28-day and hospital mortality in patients aged < or ≥ 65. Significant difference compared with the patients aged < 65 was determined. *n* = 395 in non-NAFLD group, *n* = 129 in NAFLD group. **(G** and **H)** 28-day and hospital mortality in patients with or without diabetes. Significant difference compared with the

non-NAFLD control was determined. n = 456 in non-diabetic group, n =68 in diabetic group. The differences between two groups were determined using Fisher's exact test. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$.

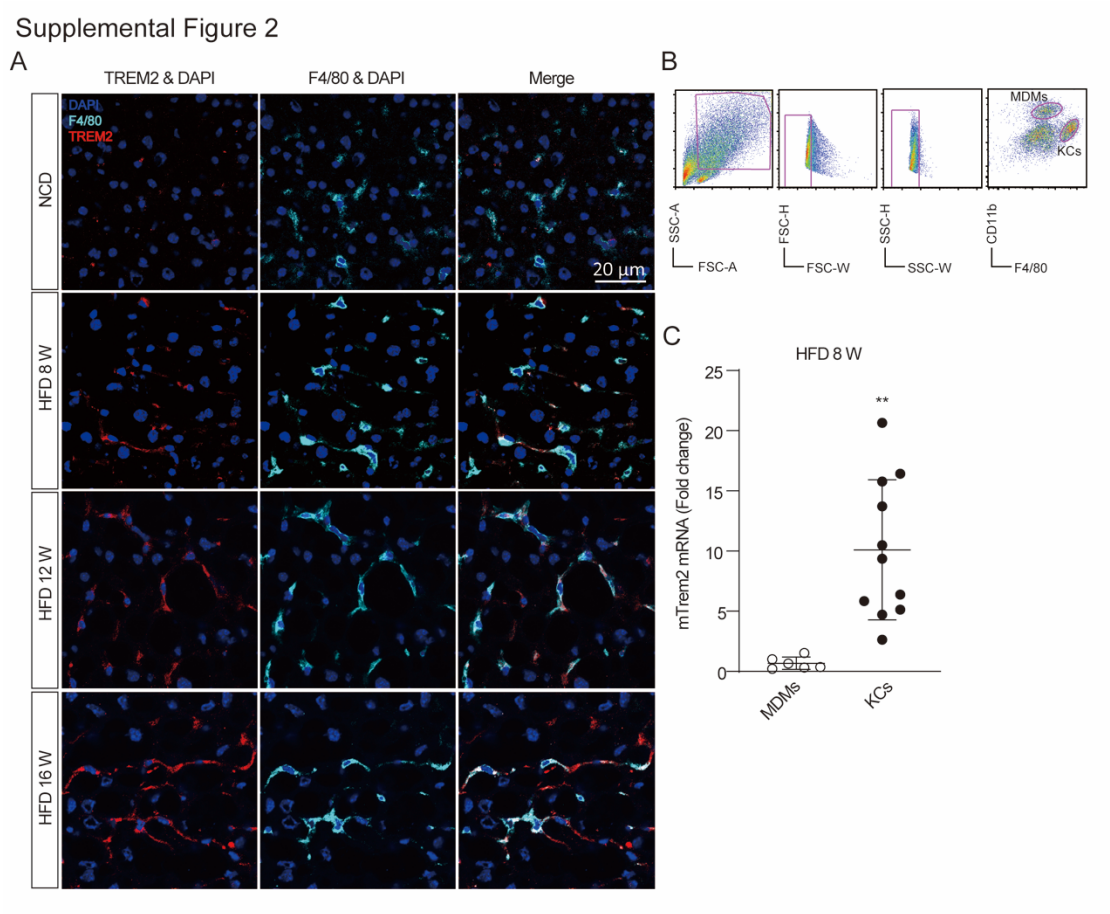

Fig. S2. Expression of TREM2 in livers of NCD- and HFD-fed WT mice. (A) Confocal images of liver sections from NCD and HFD WT mice show TREM2 (Red), F4/80 (Cyan) and DAPI staining. Representative of 3 experiments. Confocal image at 40X was taken with a Nikon A1 inverted fluorescent microscope. Scale bar, 20 μm. **(B)** Representative FACS plot showing the strategy to enrich the Kupffer cells (KCs) and Monocyte-derived macrophages (MDMs). **(C)** qPCR analysis for MDMs and KCs *Trem2* expression in 8 weeks HFD-fed WT mice. Mouse *Trem2* (mTrem2) expression was normalized to GAPDH mRNA levels. n = 6 in MDMs group; n = 11 in KCs group. Data are shown as the mean ± SD. Data were analyzed by an unpaired, 2-tailed Student's t test. $^{**}P < 0.01$.

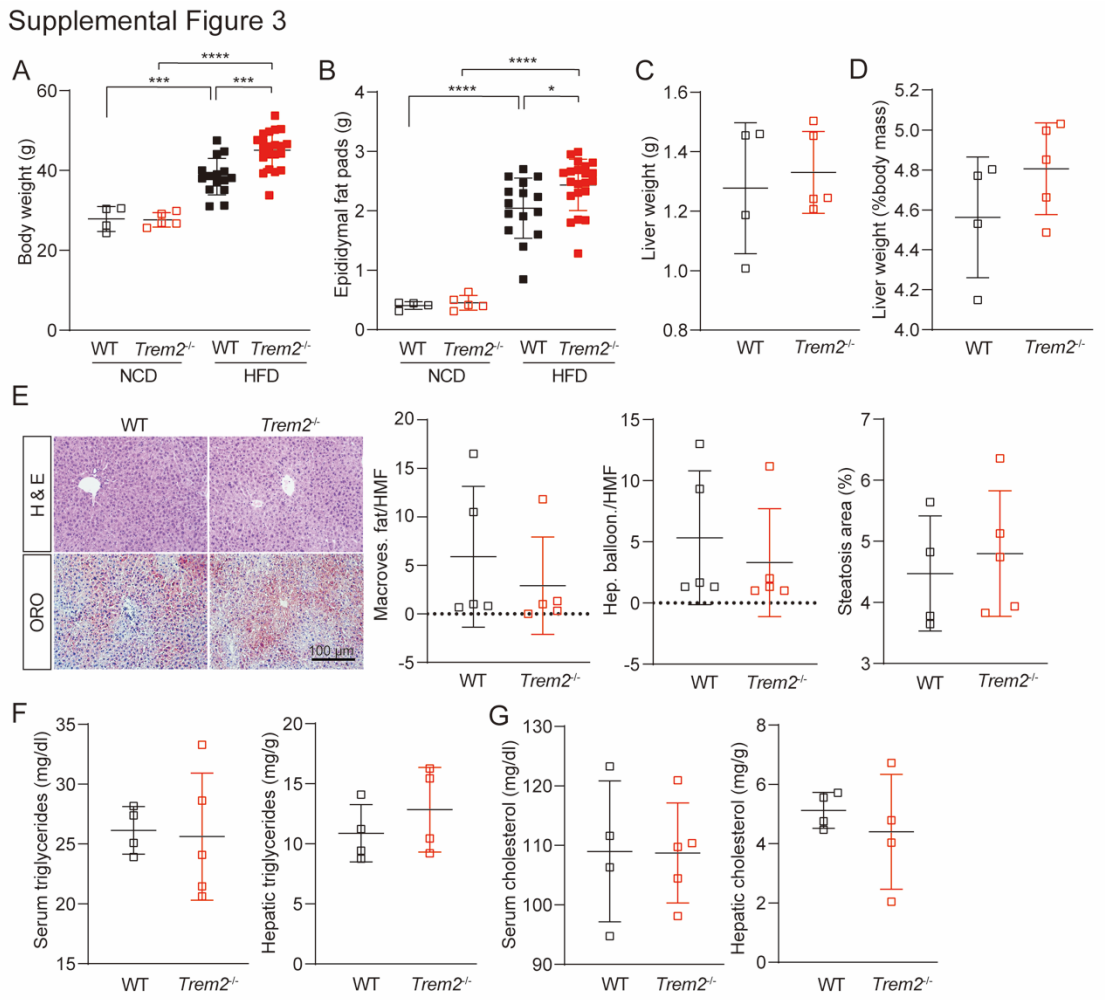

Fig. S3. Characteristics of HFD-fed or NCD-fed WT and *Trem2*$^{-/-}$ mice. (A and **B)** Body weight **(A)** and epididymal pads weight **(B)** of WT and *Trem2*$^{-/-}$ mice after either 8-week NCD feeding or HFD feeding. *n* = 4 for NCD WT mice, *n* = 5 for NCD *Trem2*$^{-/-}$ mice, *n* = 15 for HFD WT mice, *n* = 21 for HFD *Trem2*$^{-/-}$ mice. **(C** and **D)** Liver weights **(C)** and liver/body weight ratios **(D)** of WT and *Trem2*$^{-/-}$ mice after 8-week NCD feeding. *n* = 4 in WT group; *n* = 5 in *Trem2*$^{-/-}$ group. **(E)** Representative images of H&E-stained and Oil red O (ORO)-stained liver sections from mice that were fed a NCD for 8 weeks. Number of hepatocytes with macrovesicular fat (macroves. fat) or hepatocyte ballooning (hep. balloon.) and percentage of ORO-positive area per high-magnification field (HMF) were determined by ImageJ from 6 fields per section. *n* = 5 per group. Scale bar, 100 μm. **(F** and **G)** Levels of triglycerides **(F)** and cholesterol **(G)** in serum (left) and livers (right) from WT and *Trem2*$^{-/-}$ mice with 8-week NCD-feeding. *n* = 4-5 per group. All data are shown as the mean ± SD. Data were analyzed by one-way analysis of variance with Bonferroni corrections **(A** and **B)**, or an unpaired, 2-tailed Student's *t* test **(C-G)**. **P* < 0.05, ****P* < 0.001, *****P* < 0.0001.

Supplemental Figure 4

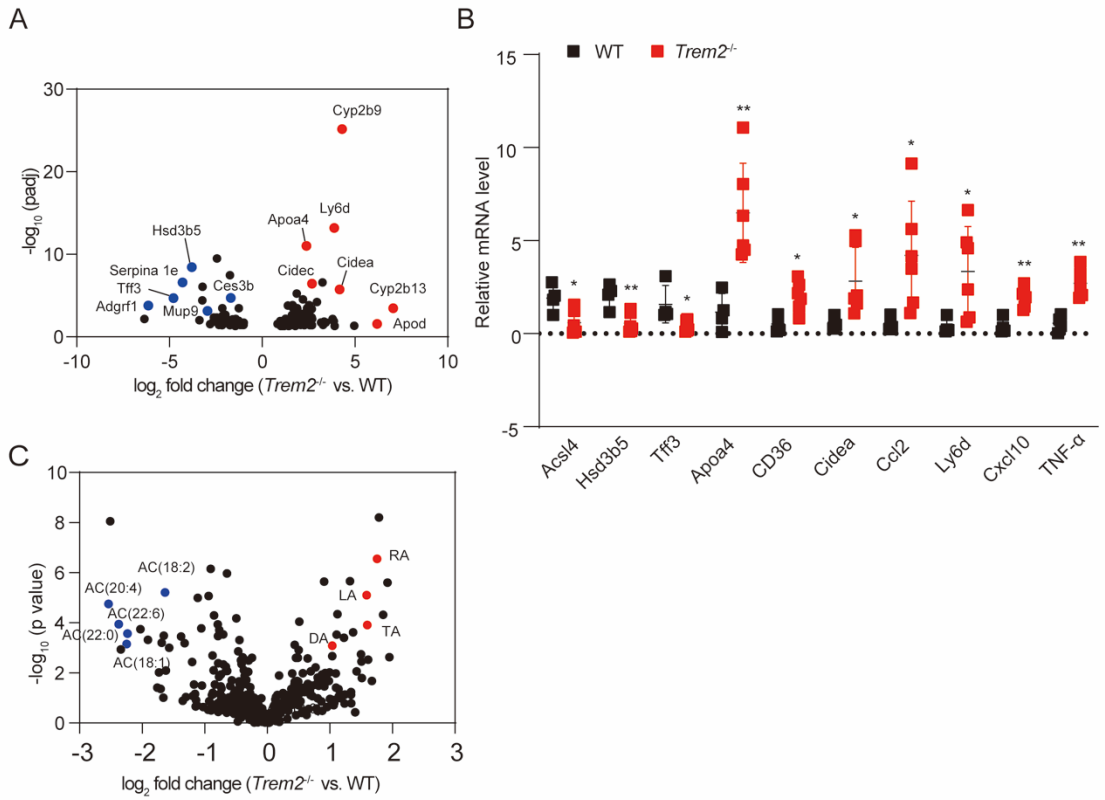

Fig. S4. *Trem2* deletion exacerbates hepatocyte lipid overload and the progression of NAFLD. (A) Volcano plot indicating the genes that were differentially expressed in RNA-seq analysis of liver samples from 8 weeks HFD-fed WT and *Trem2*$^{-/-}$ mice, *n* = 3 mice per group. red, upregulated genes; blue, downregulated genes, *Padj* < 0.05. **(B)** qPCR analysis for the expression of the indicated genes associated with metabolic fates, lipogenesis and inflammatory cytokine secretion in livers isolated from mice that were fed a HFD for 8 weeks. Gene expression was normalized to β-actin mRNA levels. *n* = 4 in WT group, *n* = 6 in *Trem2*$^{-/-}$ group. **(C)** The pattern of multiple lipid species and lipid derived metabolites in the liver extracts from 8-week HFD-fed WT and *Trem2*$^{-/-}$ mice after an overnight fast. red, upregulated lipids; blue, downregulated lipids, *P* value < 0.05. Data are presented as the mean ± SD. Significance was determined by an unpaired, 2-tailed Student's *t* test. **P* < 0.05, ***P* < 0.01. RA, ricinoleic acid; LA, linoleic acid; DA, dodecanedioic acid; TA, 9,10,13-trihydroxystearic acid; AC, acylcarnitine.

Supplemental Figure 5

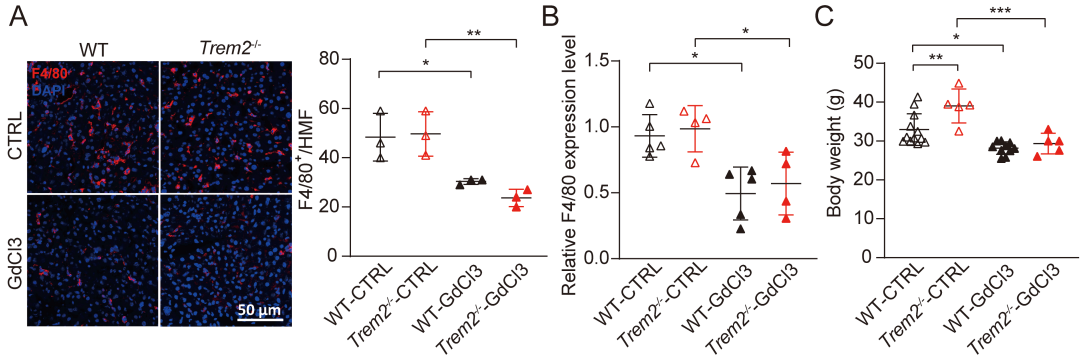

Fig. S5. Liver KCs depletion by GdCl3. (A) Confocal images of liver sections from GdCl3 or control (CTRL)-treated livers show the macrophage marker F4/80 (red) and DAPI nuclear staining (blue). Confocal image at 40X was taken with a Nikon A1 inverted fluorescent microscope. F4/80-positive cells were determined by ImageJ. *n*=3 per group. Scale bar, 50 μm. **(B)** qPCR analysis of mouse F4/80 expression in livers after GdCl3 or CTRL treatment. Gene expression was normalized to β-actin mRNA levels. *n* = 5 in WT CTRL and WT GdCl3 group; *n* =4 in *Trem2*$^{-/-}$ CTRL and *Trem2*$^{-/-}$ GdCl3 group. **(C)** Body weights of WT and *Trem2*$^{-/-}$ mice fed with HFD and treated with GdCl3 or CTRL. *n* = 12 in WT CTRL group; *n* =5 in *Trem2*$^{-/-}$ CTRL group; *n* =10 in WT GdCl3 group; *n* =5 in *Trem2*$^{-/-}$ GdCl3 group. Data are presented as the mean ± SD. The data were analyzed by one-way analysis of variance with Bonferroni corrections for multiple comparisons. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

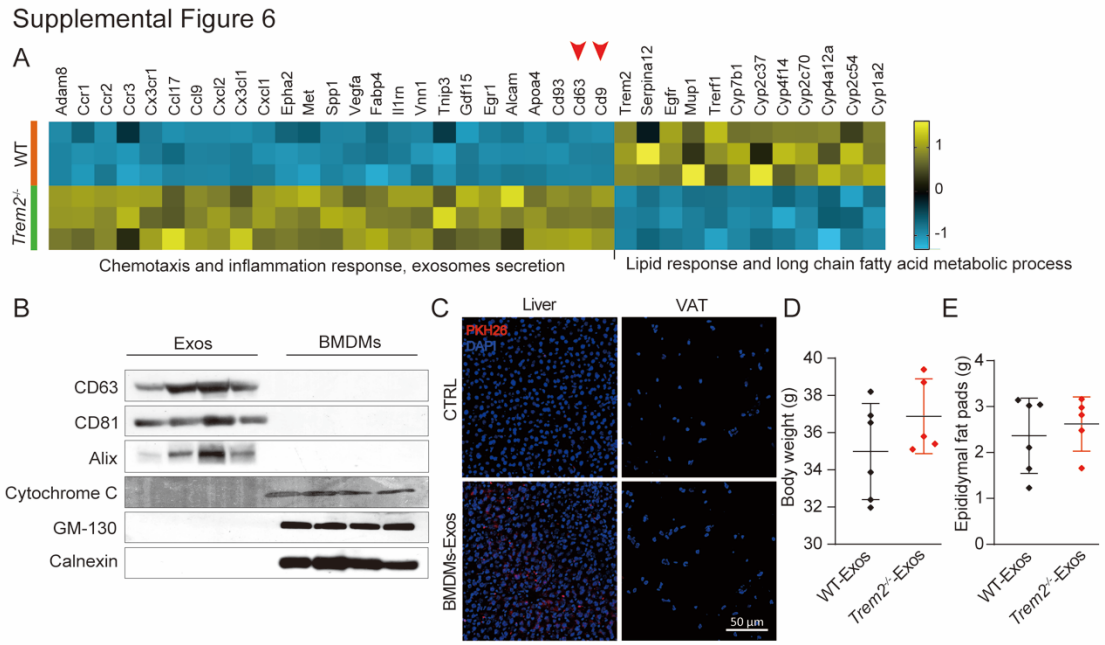

Fig. S6. *Trem2* deletion leads to changes in macrophage-Exos numbers and contents. (A) Heat map showing KCs expression pattern of differentially expressed genes (Fold change⩾2, *Padj* < 0.05). *n* = 3 per group. **(B)** Representative western blotting shows the exosome makers (CD63, CD81, Alix), mitochondria maker (cytochrome c), Golgi marker (GM130) and endoplasmic reticulum maker (calnexin) on bone marrow-derived macrophages (BMDMs) and exosomes (Exos) isolated from BMDMs. *n*=4 per group. **(C)** Representative fluorescence pictures show the BMDM-Exos distribution 16 h after tail vein injection. Red: exosomes labeled by PKH26, blue: DAPI. Representative of 2 experiments. Scale bar, 50 μm. **(D** and **E)** Body weight **(D)** and epididymal pads weight **(E)** of WT mice with either WT Exos or *Trem2*$^{-/-}$ Exos treatment. *n* = 6 in WT-Exos group; *n* = 5 in *Trem2*$^{-/-}$-Exos group. Data are presented as the mean ± SD. The data were analyzed by an unpaired, 2-tailed Student's *t* test. VAT: visceral adipose tissue.

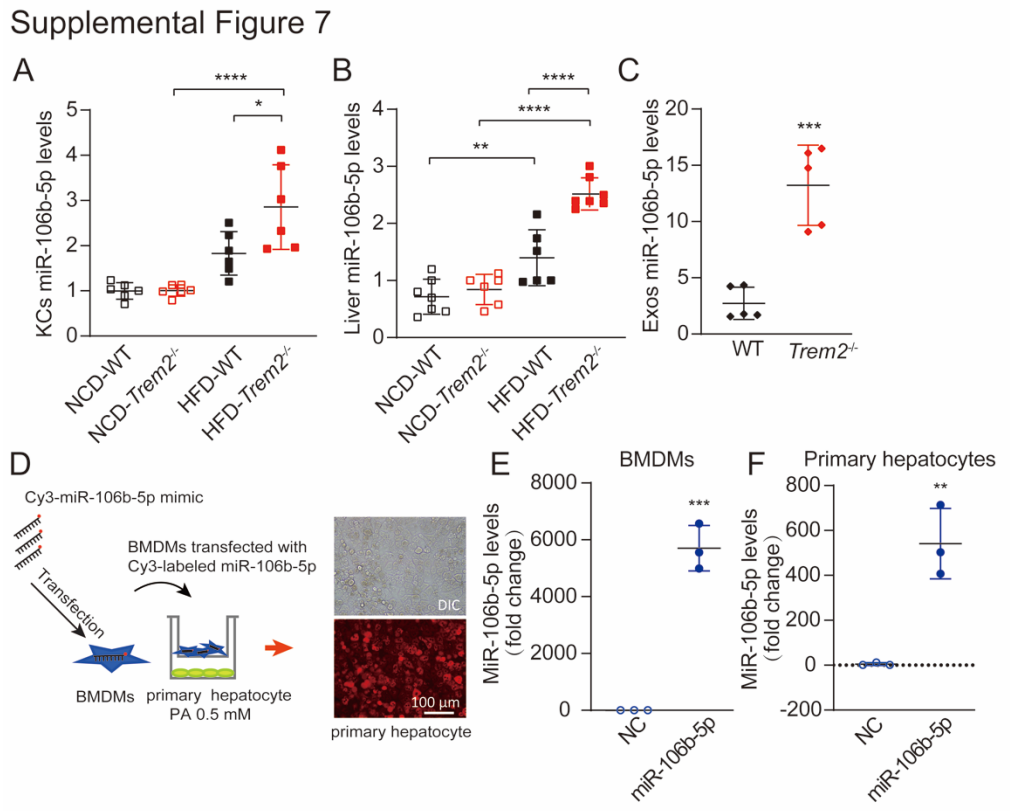

Fig. S7. *Trem2* deletion leads to changes in macrophage-Exos miRNA-106b-5p content. (A and **B)** qPCR analysis of miR-106b-5p expression in KCs (**A**, *n* = 6 per group), and livers (**B**, *n* = 7 in NCD WT group; *n* = 6 in NCD *Trem2*$^{-/-}$ group; *n* = 6 in HFD WT group; *n* = 7 in HFD *Trem2*$^{-/-}$ group) from 8-week NCD-fed or HFD-fed WT and *Trem2*$^{-/-}$ mice. Gene expression was normalized to U6 levels. **(C)** qPCR analysis for miR-106b-5p content in Exos from WT and *Trem2*$^{-/-}$ BMDMs after PA (0.5 mM) stimulation for 12 h. *n* = 5 per group. Gene expression was normalized to U6 levels. **(D-F)** BMDMs transfected with a Cy3-labeled miR-106b-5p mimic were co-cultured with WT primary hepatocytes in a transwell plate **(D)**. qPCR analysis for the expression of the miR-106b-5p in BMDMs after transfection **(E)** and in hepatocytes after co-culture with BMDMs for 12 h **(F)**, *n* = 3 per group. Data are presented as the mean ± SD. The data were analyzed by the one-way analysis of variance with Bonferroni corrections for multiple comparisons **(A** and **B)**, or an unpaired, 2-tailed Student's *t* test **(C, E** and **F)**. **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.0001. DIC, differential interference contrast.

Supplemental Figure 8

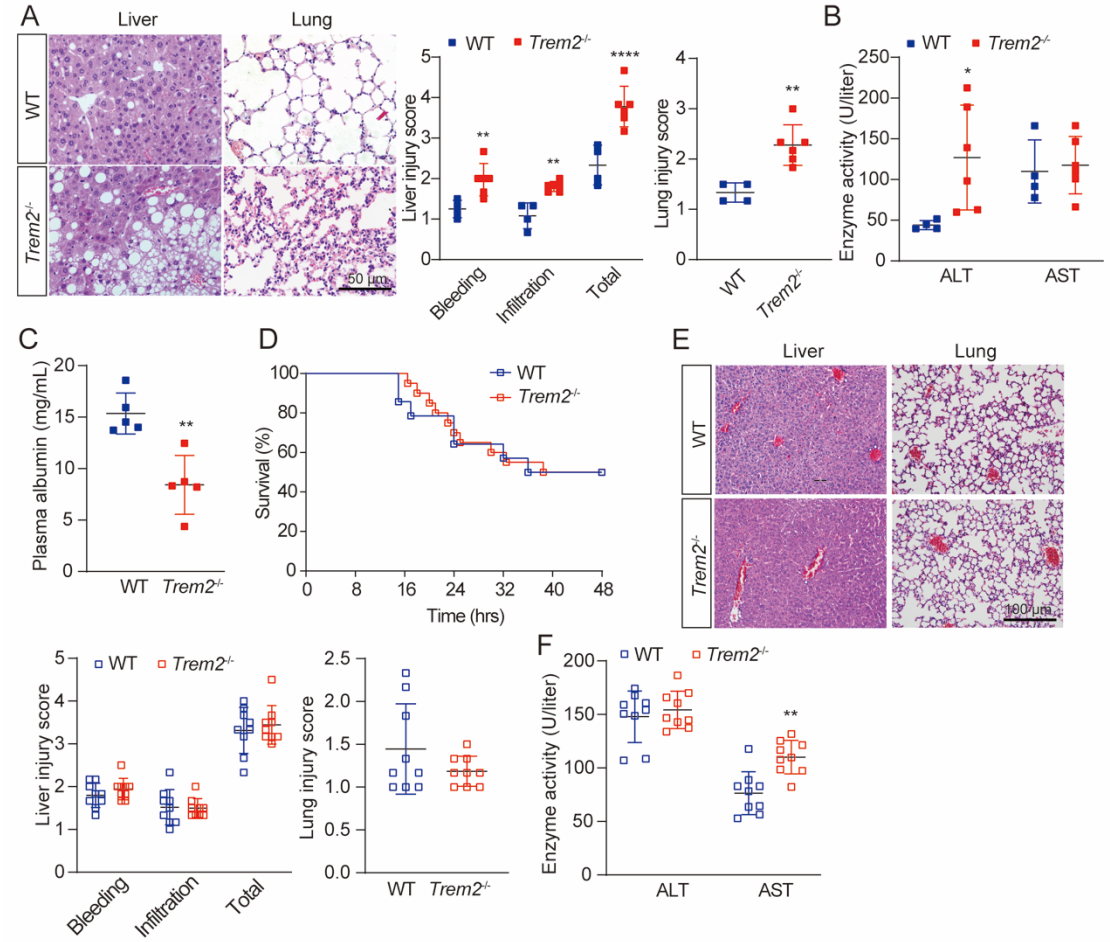

Fig. S8. Deletion of *Trem2* increases the susceptibility of HFD-fed mice to sepsis-induced organs dysfunction. (A-C) Organs function test in cecal ligation and puncture (CLP) model. At 24 h post-CLP, livers and lungs were collected for H&E staining **(A),** and plasma was collected for ALT, AST and albumin level test **(B** and **C)** in HFD group. *n* = 4-6 per group. Scale bar, 50 μm. **(D-F)** Survival and organ injury evaluation in LPS challenged mice. Age-matched male NCD-fed WT and *Trem2*$^{-/-}$ mice were intraperitoneally injected with LPS (10mg/kg). Mice survival was monitored every 8 h **(D)**. *n* = 14 for NCD WT mice, *n* = 20 for NCD *Trem2*$^{-/-}$ mice. **(E)** At 12 h post-LPS, livers and lungs were collected for H&E staining. *n* = 9 for each group. Scale bar, 100 μm. (**F**) ALT, AST levels in plasma were determined at 12 h post-LPS. *n* = 9 for each group. Data are presented as the mean ± SD. The data were analyzed by an unpaired, 2-tailed Student's *t* test **(A, B, C, E** and **F)**, or Log-rank test **(D)**. **P* < 0.05, ***P* < 0.01, *****P* < 0.0001.

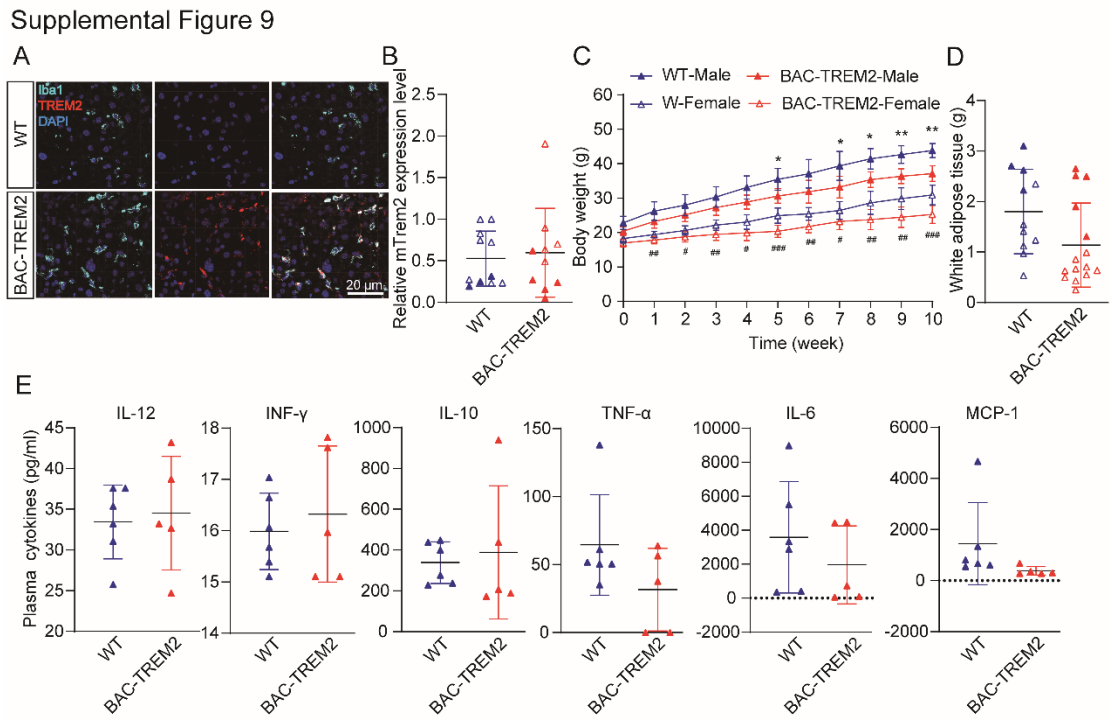

Fig. S9. Overexpression of TREM2 in liver macrophages reduces steatohepatitis and sepsis-induced liver injury. (A) Confocal images of liver sections 10-week post HFD. Human TREM2 (Red), the macrophage marker Iba1 (Cyan) and DAPI nuclear staining. Confocal image at 60X was taken with a Nikon A1 inverted fluorescent microscope. Representative of 2 experiments. Scale bar, 20 μm. **(B)** qPCR analysis for the liver expression of mouse *Trem2* at 10-week post HFD. Gene expression was normalized to β-actin mRNA levels. n = 11 in WT group, n = 10 in BAC-TREM2 group. Filled and open symbols refer to male and female, respectively. **(C)** Body weight changes over time on the HFD. n = 11 in WT group; n = 15 in BAC-TREM2 group. Filled and open symbols refer to male and female, respectively. Significant difference compared with the WT male (*) or WT female ($^{\#}$) was determined, respectively. **(D)** White adipose weight of BAC-TREM2 and WT littermates with 10-week HFD feeding. n = 11 in WT group; n = 15 in BAC-TREM2 group. Filled and open symbols refer to male and female, respectively. **(E)** Cytokine test at 24 h post-cecal ligation and puncture (CLP). Male BAC-TREM2 and WT mice were fed with HFD for 10 weeks. After dietary intervention, mild polymicrobial sepsis was induced by CLP. The plasma cytokine markers were quantified by mouse inflammation kit (BD Cytometric bead array) at 24 h post-CLP. n = 6 in WT group; n = 5 in BAC-TREM2 group. Data represent mean ± SD. The data were analyzed by an unpaired, 2-tailed Student's t test. *$P < 0.05$, **$P < 0.01$; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$; $^{\#\#\#}P < 0.001$.

Table S1: ICU Patients characteristics

Characteristics	Patients with non-NAFLD (n = 395)	Patients with NAFLD (n =129)	*P* value
Age (yr)	63.84±16.13	57.35±16.65	<0.001
Sex, male (%)	221 (56%)	69 (53%)	0.63
BMI	22.7±3.84	25.02±4.37	<0.001
SOFA score	6.13±3.53	8.39±4.49	<0.001
APACHE II	14.28±5.26	15.94±6.49	0.0035
Sepsis due to			0.001
Peritonitis	287 (72.66%)	74 (57.36%)	
Pneumonia	62 (15.7%)	23 (17.83%)	
Urinary tract infections	9 (2.28%)	4 (3.1%)	
Others	37 (9.37%)	28 (21.71%)	
Liver enzymes			
ALT (IU/L)	103.19±386.38	185.75±638.95	0.08
AST (IU/L)	145.04±456.3	167.78±756.41	0.07
Total bilirubin (mg/dL)	38.69±118.5	40.05±50.15	0.90
Coagulation function			
PT (s)	16.28±3.95	16.13±4.6	0.72
APTT (s)	44.53±16.74	44.17±18.51	0.83
TT (s)	16.99±8.69	18.44±8.0	0.09

Plasma fibrinogen	4.04±1.88	4.86±7.95	0.057
Comorbidities			
Type 2 diabetes	32 (8.1%)	36 (27.91%)	<0.001
Hypertension	81 (20.51%)	31 (24.03%)	0.39
Medicine			
Vasoactive drugs	257 (65.06%)	84 (67.44%)	>0.999
Immunomodulator drugs	147 (37.22%)	73 (56.59%)	0.0001
Medical support			
Ventilation	164(41.52%)	103(79.84%)	<0.001
Renal replacement therapy	100 (25.32%)	61 (47.29%)	<0.001
Blood glucose (mg/dL)	8.4±3.36	9.72±4.14	0.0003
Length of ICU stay	11.22±17.92	16.09±19.11	0.0086
28-day mortality	62 (15.7%)	42 (32.56%)	<0.001
Hospital mortality	73 (18.48%)	48 (37.21%)	<0.001

Data are expressed as the mean ± SD. or number (%) where applicable. Significance was determined by an unpaired, 2-tailed Student's *t* test or Fisher's exact test.

BMI: body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PT: prothrombin time; APTT: active partial thromboplastin time; TT: thrombin time; APACHE II = Acute Physiology and Chronic Health Evaluation II; ICU = intensive care unit; SOFA = Sequential Organ Failure Assessment.

Table S2: Characteristics of the donors who underwent organ donation after cardiac death (DCD)

	Non-NAFLD (9)	NAFLD (21)	*P* value
Age (yr)	44.56±14.48	44.86±10.73	0.95
Sex, male (%)	6 (66.67)	13 (61.90)	0.80
Liver steatosis area (%)	2.5±1.50	39.44±21.96	<0.001
Liver lobular inflammation score	0.33±0.50	1.95±0.74	<0.001
Liver ballooning score	0.22±0.44	1.95±0.70	<0.001
ALT (IU/L)	45.56±22.0	81.38±43.08	0.026
AST (IU/L)	45.22±26.1	90.48±55.61	0.028

Data are expressed as the mean ± SD. or number (%) where applicable. Significance was determined by an unpaired, 2-tailed Student's *t* test or Fisher's exact test.

NAFLD: nonalcoholic fatty liver disease; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Table S3: Primers for Polymerase Chain Reaction

Gene	Sequence (from 5' to 3')
Human β-actin	Forward primer- AGAAAATCTGGCACCACACC
	Reverse primer- AGAGGCGTACAGGGATAGCA
Human TREM2	Forward primer- ATCCCTGCCCAGTCCACCCTTGATGGCT
	Reverse primer- CCATCCTTCTCCTCCTGGCCTGCATCTTT
mouse β-actin	Forward primer- CTACAATGAGCTGCGTGTG
	Reverse primer- GCGTGAGGGAGAGCATAG
mouse GAPDH	Forward primer- CGACTTCAACAGCAACTCCCACTCTTCC
	Reverse primer- TGGGTGGTCCAGGGTTTCTTACTCCTT
mouse Trem2	Forward primer- CACTCTGAAGAACCTCCAA
	Reverse primer- TGACCCACAGGATGAAAC
mouse Acsl4	Forward primer- TGGAAGTCCATATCGCTCTGT
	Reverse primer- TTGGCTACAGCATGGTCAAA
mouse Hsd3b5	Forward primer- CTACTGGATGCTTGTGTG
	Reverse primer- CTGTATGGGTATGGGTTAG
mouse Tff3	Forward primer- CCTCTGGCTAATGCTGTT
	Reverse primer- TGGGATACTGGAGTCAAAG
mouse Apoa4	Forward primer- ATCCAGTGTAGCCGAAAC
	Reverse primer- GACATCCGTCTTCTGAAAC
mouse CD36	Forward primer- GATGACGTGGCAAAGAACAG
	Reverse primer- TCCTCGGGGTCCTGAGTTAT
mouse Cidea	Forward primer- GAATAGCCAGAGTCACCTT
	Reverse primer- GGACATAAACCTCAGCAG
mouse Ccl2	Forward primer- AGGTCCCTGTCATGCTTCTG
	Reverse primer- TCTGGACCCATTCCTTCTTG
mouse Ly6d	Forward primer- GCCAACTGTAAGAACCCT
	Reverse primer- ATTGTGTGACCTCGGAAC
mouse Cxcl10	Forward primer- GACGGTCCGCTGCAACTG

	Reverse primer- CTTCCCTATGGCCCTCATTCT
mouse TNF-α	Forward primer- TACTGAACTTCGGGGTGATTGGTCC
	Reverse primer- CAGCCTTGTCCCTTGAAGAGAACC
Mouse F4/80	Forward primer- CTGCCCTAAGTATTCCAAC
	Reverse primer-TCTTCACAGGATTCGTCC

Dataset S1 (separate file).

List of differentially expressed genes between human non-NAFLD and NAFLD livers.

Dataset S2 (separate file).

List of differentially expressed genes between WT and *Trem2*$^{-/-}$ livers after 8-week HFD feeding.

Dataset S3 (separate file).

List of identified positive and negative lipids in WT and *Trem2*$^{-/-}$ livers after 8-week HFD feeding.

Dataset S4 (separate file)

List of differentially expressed genes between WT and *Trem2*$^{-/-}$ Kupffer cells (KCs) after 8-week HFD feeding.

Dataset S5 (separate file)

List of differentially expressed small RNA between WT and *Trem2*$^{-/-}$ Kupffer cells (KCs) after 8-week HFD feeding.